THE American Journal OF Gastroenterology

VOL. 31, NO. 2 AUGUST, 1959

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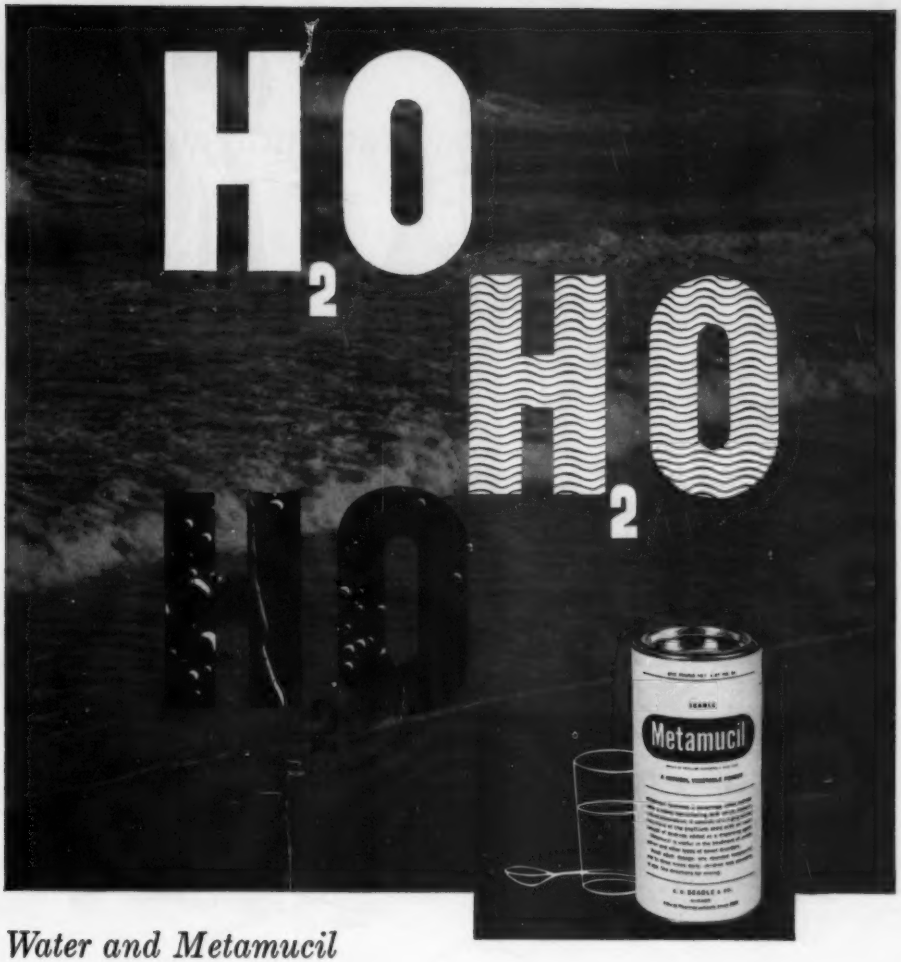

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contents:

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Pylorospasm or cardiospasm	11	2
Irritable bowel	11	—
Biliary tract dysfunctions	11	1
Miscellaneous	7	29
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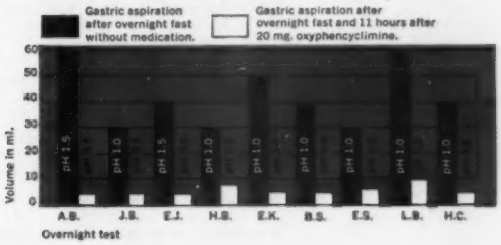

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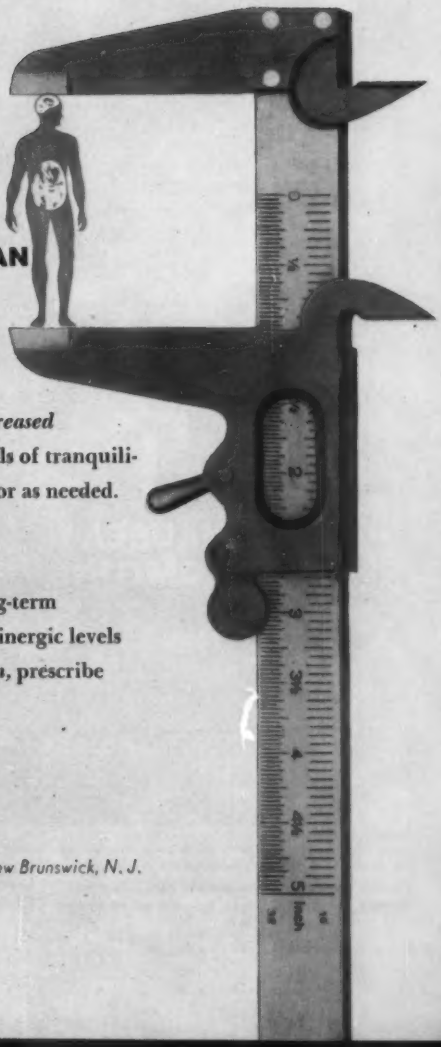

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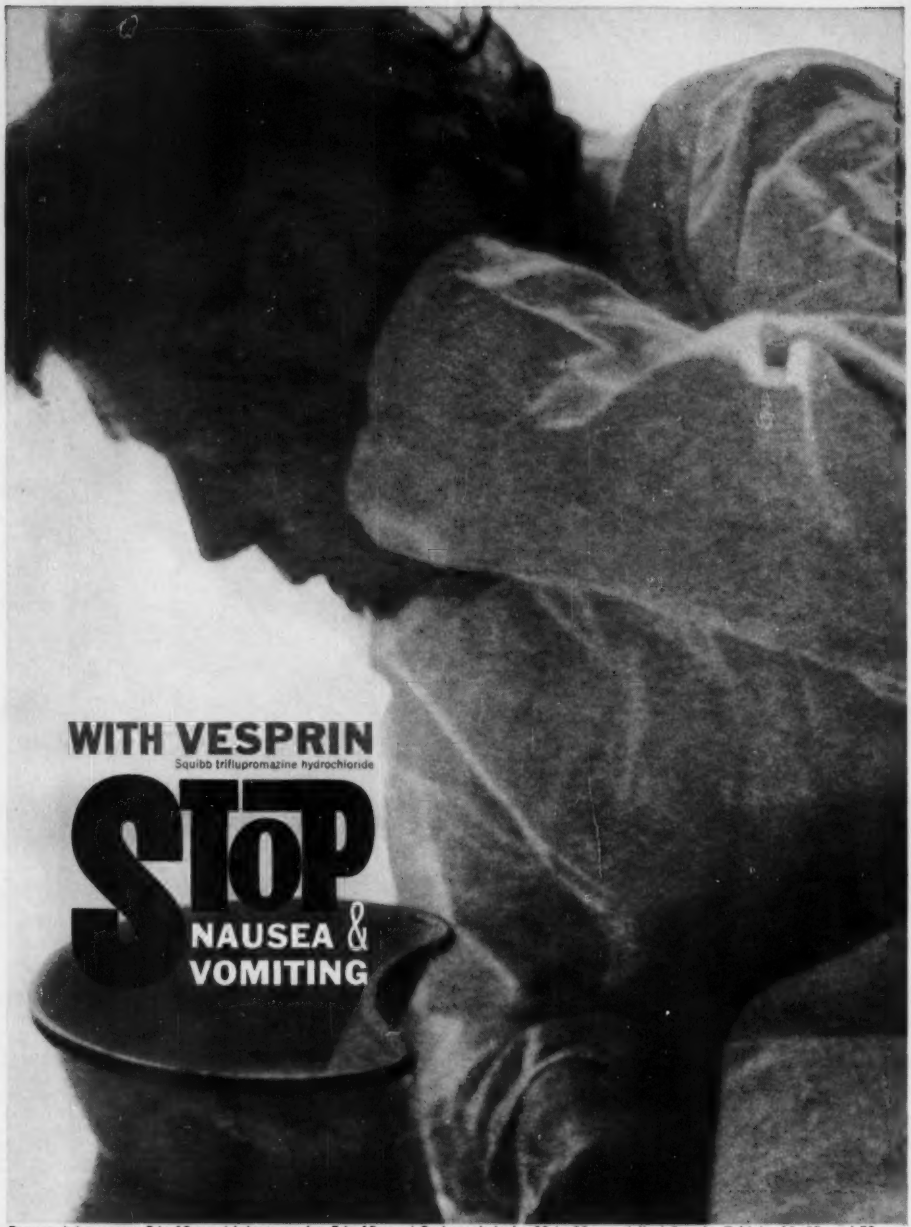

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1. Grayzel, H. G., Heimer, C. B., and Grayzel, R. W.: New York St. J. Med. 53:2233, 1953. **2.** Heimer, C. B., Grayzel, H. G., and Kramer, B.: Archives of Pediatrics 68:382, 1951. **3.** Behrman, H. T., Combes, F. C., Bobroff, A., and Leviticus, R.: Ind. Med. & Surgery 18:512, 1949. **4.** Turell, R.: New York St. J. Med. 50:2282, 1950. **5.** Marks, M. M.: Missouri Med. 52:187, 1955.

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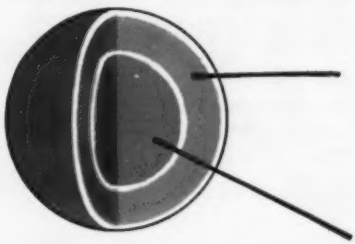

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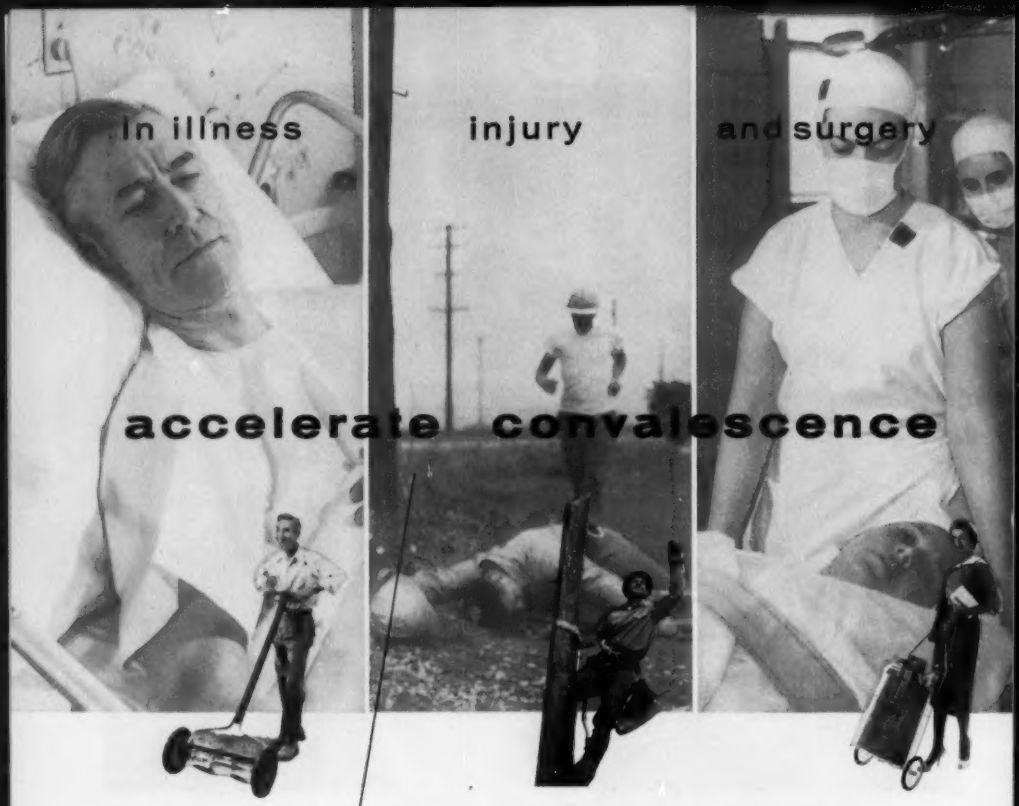

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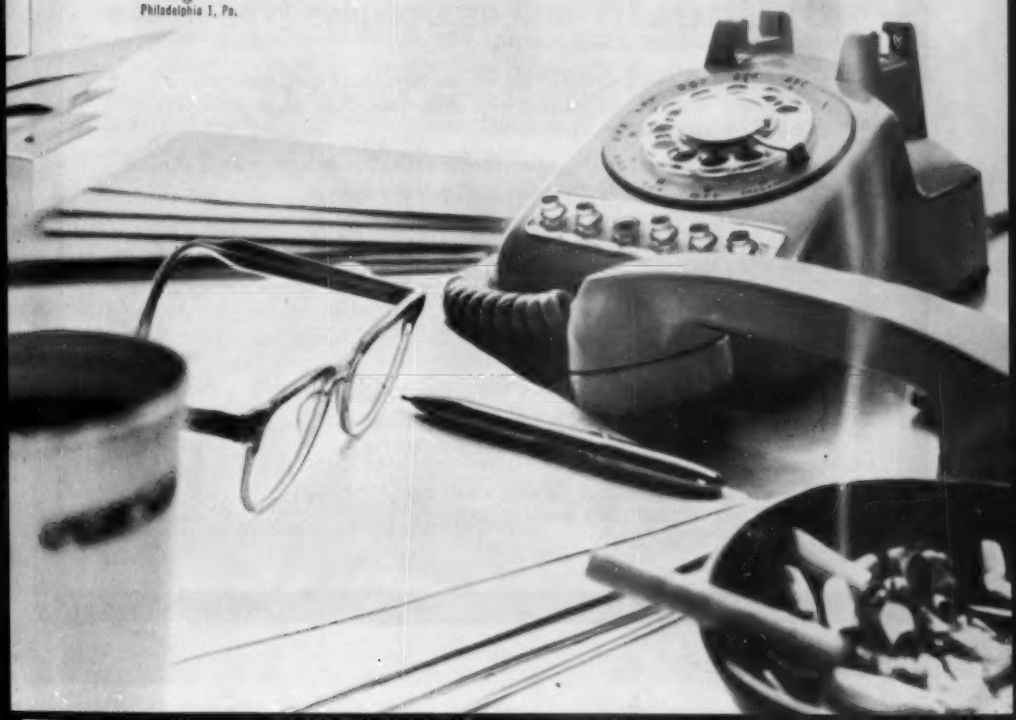

THE American Journal OF Gastroenterology

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VOLUME 32 AUGUST, 1959 NUMBER 2

GIANT ULCERS OF THE STOMACH*

ISIDORE COHN, JR., M.D., D.Sc. (Med.), F.A.C.G.
JACK SARTIN, M.D.
and
PERRY SUDDUTH, M.D.
New Orleans, La.

Current medical literature favors the view that the incidence of cancer increases with the size of a gastric ulcer. Since our limited personal experience did not substantiate this opinion, it was decided to review the local and recorded experience to re-assess the validity of a time-honored, but perhaps incorrect, medical "fact".

This study was restricted to those large gastric ulcers, over 2.5 cm. in diameter, which would create diagnostic problems for the clinician, radiologist, gastroscopist, surgeon, and even for the pathologist (Figs. 1 and 2). Obvious gastric carcinomas create no diagnostic problems and are not considered here. But the true ulcer, whose benign or malignant character may be determined only under the microscope interests us because its correct diagnosis poses a challenge for all concerned in its management.

On this basis we collected all *gastric ulcers* seen at Charity Hospital from June, 1950 to August, 1958 provided there was a pathologic report stating that the diameter of the ulcer was 2.5 cm. or more. No other criteria were utilized in selecting cases for study. After a review of all charts with a diagnosis of gastric ulcer, carcinoma, sarcoma, or other miscellaneous gastric lesions, 48 acceptable cases were found. Forty of these were benign giant gastric ulcers.

In discussing these lesions some authors have chosen to call them giant ulcers, some simply call them large ulcers. Nowhere is there agreement on the

*Presented before the Course in Postgraduate Gastroenterology of the American College of Gastroenterology, New Orleans, La., 23, 24, 25 October 1958.

Department of Surgery, Louisiana State University School of Medicine, New Orleans, La. and Charity Hospital of Louisiana at New Orleans.

minimum size for either a "large" ulcer or a "giant" one, but the selection of a 2.5 cm. minimum diameter restricts this study to the size range where a high incidence of carcinoma has been reported.

History and Physical Findings

The age distribution was as expected for chronic ulcer disease, with the greatest incidence in the decade between 50 and 59 (Fig. 3). Surprisingly, large ulcers were found in both the young and the old. The predominance of males (Table I) is in keeping with the usual incidence of ulcer disease. The almost identical distribution between white and colored in both sexes suggests a greater incidence of the disease in the white race, in view of the greater percentage of colored admissions to the hospital during this period.

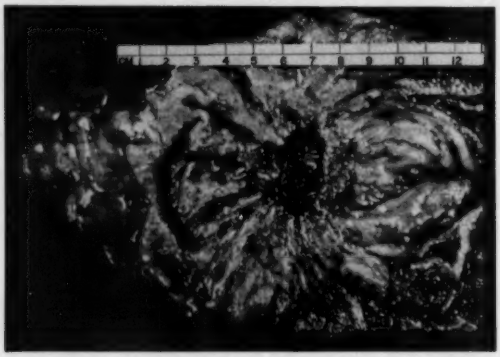

Fig. 1—One of resected specimens of giant gastric ulcers which originally aroused interest in this subject. This was a benign lesion. (Reproduced by permission from *Annals of Surgery* **147**:749, 1958).

The size of the ulcer and the reaction surrounding it suggest a chronicity of disease which is borne out by the history of ulcer symptoms. Over half the patients had symptoms for one year or longer, and almost one-third had symptoms for over five years. Ten patients reported symptoms for 10 to 34 years.

The presenting symptoms were not significantly different from those of patients with peptic ulcers in general. Epigastric pain as the chief complaint of 36 patients was the commonest chief complaint, but was noted altogether by 41 patients. Vomiting, noted by 45 patients, was the most commonly recorded symptom, followed by nausea in 42 patients. Hematemesis and melena were next, followed by weight loss, which ranged from five to 50 pounds in 21 patients. Relief from milk in 14 patients was an unexpected finding in view of the size of their ulcers.

Twenty-seven patients had previous treatment for gastrointestinal disease, including three with previous perforations.

Physical findings were generally of no specific help except in those admitted with either an acute perforation or massive bleeding. An abdominal mass was palpated in four patients, each of whom was thought to have a carcinoma, although each was found to have a benign ulcer.

Preoperative Study

Gastric analysis was performed on 21 patients. Four patients with malignant ulcers had no free acid on fasting specimens, but a fifth one had 45 units of free

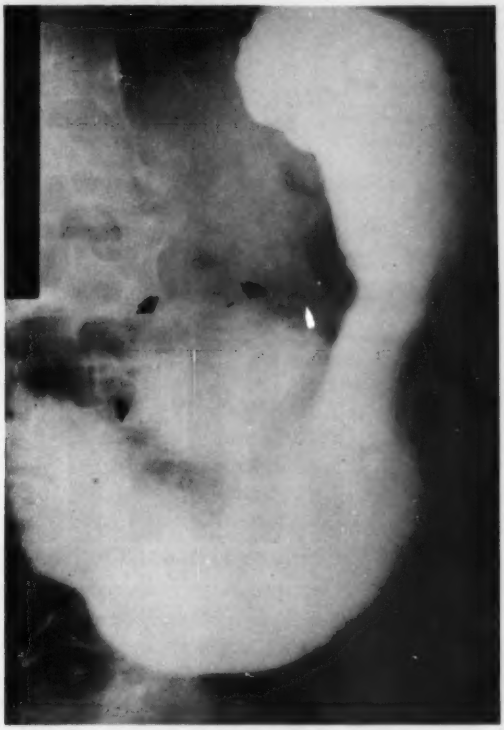

Fig. 2—X-ray of stomach, showing giant ulcer on lesser curvature. This lesion was subsequently found to be benign and this was one of the patients that stimulated interest in this review.

acid and 70 units of total acid. Of the 16 patients with benign ulcers who had gastric analyses, four had no free acid and 12 had free and total acid ranging respectively to 52 and 72 units.

Roentgenologic studies of the stomach and duodenum were obtained on 37 patients. Five patients were not subjected to barium studies because of perfora-

tion and six were not so studied because of bleeding. Within the past two years, five patients with a chief complaint of hematemesis were subjected to emergency upper gastrointestinal x-rays as a result of more recent thinking that x-rays will provide important diagnostic assistance in such critical cases. While the radiologist made the correct diagnosis in only one of these and a reasonably correct one in one other, the report of gastric or duodenal pathology in four of the five cases unquestionably aided in the management of their massive hemorrhage.

The difficulty in arriving at a correct x-ray diagnosis was not eliminated even for those cases studied electively (Fig. 4). The radiologic error made most frequently was the incorrect diagnosis of a benign lesion as a malignant one.

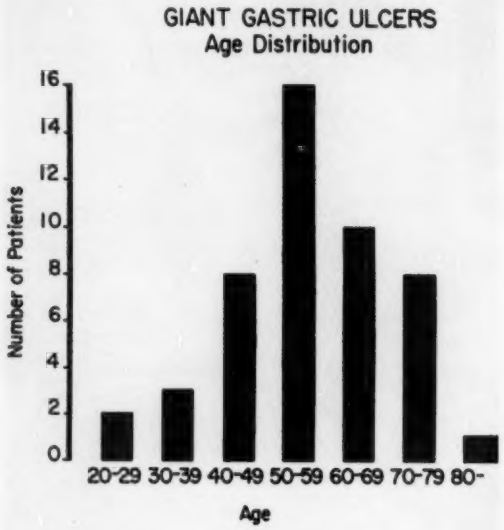

Fig. 3

This probably represents another facet of the commonly accepted dictum that all large gastric ulcers are malignant. The radiologist had an over all accuracy of 30 per cent in differentiating benign from malignant lesions.

An error in roentgenologic diagnosis in lesions of this size is more understandable than is the failure to visualize the lesion, and the 10 cases in which no gastric ulceration was reported have been reviewed in further detail. Three patients were reported to have duodenal ulcers but no gastric pathology. One of these did have duodenal scarring, but also had both 2.5 cm. and 1 cm. benign gastric ulcers. The larger of these was on the anterior surface of the lesser curvature of the antrum, as were the 2.5 cm. carcinomas in each of the other patients, neither of whom had any duodenal pathology. One patient was prop-

erly reported to have a phytobezoar and another to have a carcinoma, and it seems likely that these two unusual findings "blinded" the radiologist to the additional presence of a large gastric ulcer. A 2.8 cm. ulcer in the antrum was missed because x-ray was "unsuccessful". A 3.0 cm. lesion of the lesser curvature was missed, but the patient was erroneously reported to have a metastasis from a known carcinoma of the cervix. A 4.0 cm. ulcer in the fundus on the lesser curvature was missed, probably on account of the difficulty in visualizing this area. Gastric hyperperistalsis was the only reported abnormality in another patient who had a 4 cm. ulcer on the lesser curvature of the antrum. Multiple x-rays over a five-year period revealed nothing in a patient who had a 4.2 cm. carcinomatous ulcer in the same area.

Gastroscopy was undertaken in five patients. A correct diagnosis was made only once, in a patient with a 4.5 cm. ulcer. Two ulcers 2.5 and 3 cm. were not seen.

Metastases to the chest were not found in the 41 patients who were specifically x-rayed for this purpose.

TABLE I

GIANT GASTRIC ULCERS

	Male	Female	Total
White	20	4	24
Colored	19	5	24
Total	39	9	48

Medical therapy was tried in 17 patients. There was no improvement in 16 and only slight improvement in one. Sixteen patients did not have a trial of medical therapy because of perforation or bleeding and 15 had no trial of medical therapy because a diagnosis of carcinoma was made.

DIAGNOSIS AND THERAPY

Since the diagnostic difficulties of the radiologist have been pointed out it is only fair to emphasize similar problems of the clinicians (Fig. 5). A glance at the confusion existing in those patients who were eventually found to have benign lesions, shows that the correct diagnosis was maintained in only one-third of the cases, that a consistently erroneous diagnosis was made in an even larger proportion of cases, and that in approximately one-third of the cases the diagnosis was switched from benign to malignant or vice versa. It seems reasonable to assume that the teaching that all large ulcers must be malignant served to confuse both the internist and the surgeon just as it had the radiologist.

Diagnostic difficulty was also encountered in the eight cases with carcinoma. Two were diagnosed correctly at all times, but three were consistently classified as benign lesions. In the three remaining lesions there was no consistent diagnosis and in one of these the surgeon labeled the lesion benign even though preoperative studies indicated it was malignant.

Because of diagnostic difficulties prior to and during the operative procedure, biopsy with frozen section diagnosis was utilized in several cases. Regional nodes were correctly diagnosed as benign disease in four patients. A correct diagnosis of benign ulcer was based upon a biopsy of the ulcer itself in four cases, including two which also had node biopsy. The lymphomatous lesion and three adenocarcinomas, however, were erroneously called benign disease, emphasizing the danger of selecting a single area for histologic diagnosis of a gastric ulcer, particularly when the ulcer is of this size.

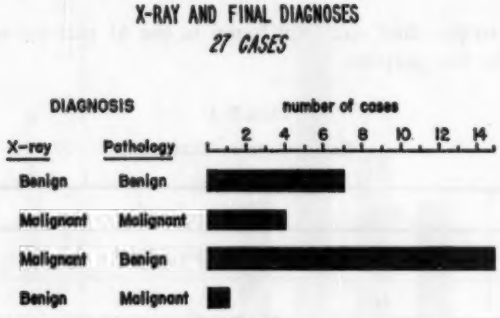

Fig. 4

Since the operating surgeon made a diagnosis of carcinoma in 23 cases with benign lesions and in four cases that did have carcinoma, it is natural that his operative approach should have been radical in over half the cases (Table II). Multiple-organ resections can only be justified in an extensive carcinomatous process, and the excessive surgery in a number of these patients speaks for the strong surgical impression of a malignant process. Within the past two years, as interest in this subject has increased, a noticeable trend toward conservatism has been present.

Postoperative Course

In spite of the extensive surgery in many poor risk patients with long-standing disease, there were 36 patients with no postoperative complications. The remaining patients had complications which ranged from a relatively minor thrombophlebitis to the complications responsible for the four deaths in the series. All four deaths occurred in males admitted with a major complication of ulcer disease—three with massive bleeding and one with a perforation. Three of

these deaths were directly related to the surgical procedures and one occurred as a result of a transfusion reaction.

Following discharge from the hospital, 27 of the 44 patients have remained asymptomatic. Of the remaining 17, six have had mild dumping, and two have had continued distress. Of the four patients who continued to lose weight, three had abdominal carcinomatosis. One patient did well for one year when he suddenly expired following the rupture of an aneurysm of the abdominal aorta. Four were lost to follow-up.

Pathologic Study

The location of these large ulcers (Fig. 6) provides no clue which will differentiate them from other gastric lesions. The majority were near the lesser

TABLE II

Operative Procedures

Subtotal gastrectomy	34
Radical subtotal combined with:	
splenectomy	6
splenectomy and/or wedge resection liver	3
splenectomy and/or pancreatectomy	2
partial resection transverse colon	1
Total gastrectomy	1
Sleeve resection	1
Closure perforation	1
Gastroenterostomy	1

curvature and/or in the antrum, the common areas for other lesions in the stomach. All the carcinomatous lesions and all but one of the largest lesions were in the antrum. Only one lesion was in the fundus.

The base of the ulcer was attached to adjacent viscera in 19 cases. The pancreas was the organ most commonly involved, and it was involved alone in six cases. The liver was involved in three cases, and the remaining cases involved various combinations of pancreas, liver, spleen, transverse colon, mesocolon, and the gastrohepatic ligament. These attachments to other viscera not only contributed to the difficulty of the surgical procedure and led to excisions of additional organs, but undoubtedly emphasized in the surgeon's mind the diagnosis of carcinoma.

The frequency of multiple gastrointestinal lesions has been striking, particularly in view of the severity of the disease processes which have been found.

In addition to the 11 patients with multiple gastrointestinal lesions, one patient with a 3 cm. benign ulcer had an abdominal aortic aneurysm. One patient had both a large gastric ulcer and a phytobezoar. Two patients had carcinoma and unrelated gastric ulcers, one having the carcinoma in the large ulcer and the other having a benign giant ulcer (5.5 cm. in diameter) and a smaller (1.5 cm.) ulcer with adenocarcinoma in it. Eight patients had multiple ulcers with a size range from 2.5 to 7 cm. for the major ulcer and from 1 cm. to 6 cm. for the secondary ulcer. One of these had three benign ulcers measuring 2, 3, and 4 cm. in diameter.

Massive Bleeding

Eleven patients, two of whom had previous similar complaints, were treated primarily because of massive gastrointestinal bleeding. Nine were males, five of whom were white. Both of the females were colored. The age range for the entire group was from 24 to 78. The chief complaint of all was vomiting, vomit-

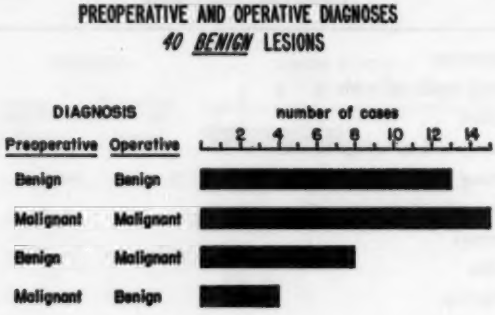

Fig. 5

ing blood, or pain. Pain was an unexpectedly common chief complaint in the presence of massive bleeding. Symptoms were noted to have been present from one day to eight years, being reported as one month or less in only three patients. It would appear that the long duration of symptoms must have reference to the abdominal distress rather than to the acute bleeding episode. Physical examination was generally negative except for evidences of bleeding. Nine patients had benign ulcers, ranging in size from 2.5 to 5.5 cm., and two patients had malignant ulcers, 2.5 and 5 cm. in diameter.

Perforation

Perforation was the direct cause for surgery in six patients, all of whom had benign lesions. The duration of symptoms ranged between one day and 15 years, but once again the prolonged histories must have been connected with their total disease rather than their presenting complaint. One had a previous per-

foration, one had a previous episode of bleeding, and two had previous gastrointestinal disorders. It is interesting to note that 15 of the 17 bleeding and perforating lesions were along the lesser curvature.

TABLE III

INCIDENCE OF CANCER IN COLLECTED SERIES OF GIANT GASTRIC ULCERS

Author	2.5 cm. and over		3.0 cm. and over		4.0 cm. and over	
	Total Cases	Number Malignant	Total Cases	Number Malignant	Total Cases	Number Malignant
Allen & Welch	21	14				
Boudreau, Harvey & Robbins	76	42	76	42	53	33
Branwood	21	0				
Caruolo, Hallenbeck & Dockerty	28	3	19	1	8	1
Gott, Shapiro & Kelty	16	0				
Grimes & Bell	32	7	32	7		
Hayes	100	33	15	6	15	6
Jennings & Richardson	11	1	11	1	10	1
Kirsh	33	9				
Ledoux-Lebard et al.	11	3	11	3	10	3
Lumsden	11	4	11	4	9	2
Marshak, Yarnis & Friedman	7	0	7	0	6	0
Marshall	108	32				
Mathieu & Moutier	3	0	3	0	3	0
Paris & Theron	13	0				
Petit-Dutaillis	7	1	7	1		
Shoulders & Lischer	7	0	7	0	7	0
Present Series	48	8	31	6	15	5
Total	553	157	230	71	136	51
Per cent Malignant	28.3		30.8		37.5	

CARCINOMA

The eight patients with malignant ulcers were evenly divided between white and colored patients, but the males predominated 3:1. The ages ranged

from 29 to 76. Each had pain as their chief complaint, present from two months to 14 years. Melena and hematemesis were each present in four, night pain in six, and nausea and vomiting in all. Response to therapy as a differential diagnostic point would have been misleading in the seven who had relief from milk. X-ray study was suggestive of gastric carcinoma in three, showed only pyloric obstruction in one, made a correct diagnosis of gastric lymphoma in one, reported duodenal ulceration in two, and reported one as normal. Frozen section diagnosis reported benign disease in the four patients so studied. In September, 1958, five and one-half years after operation, the patient with the lymphoma was asymptomatic and without evidence of recurrence. One patient was doing well two and one-half years after surgery. One is known to have died of widespread metastases three months after operation, four were deteriorating when last seen, and one was lost to follow-up immediately after discharge from the hospital.

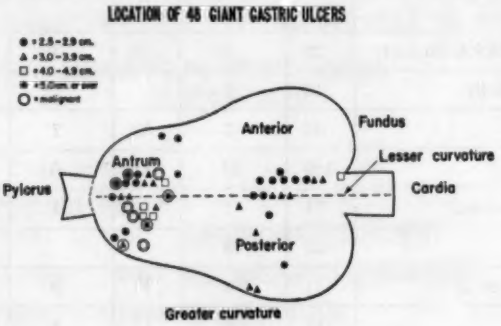

Fig. 6

Comment

Review of the cases for an eight-year period from a large volume of patient material provided an opportunity to study 48 patients with large or giant gastric ulcers. This review failed to provide any criteria by which one could differentiate a giant ulcer from the usual gastric ulcer. The long duration of symptoms is of interest, but one often sees patients with ulcer disease who have prolonged distress and it is unlikely that this one point would make the diagnosis of a giant ulcer. There are no differentiating points of age, sex, color, x-ray study, gastroscopic study, gastric analysis, location of the ulcer, or occurrence of complications that serve to distinguish these lesions from other gastric ulcers. The failure of all of the usual diagnostic studies to provide a definitive diagnosis emphasizes the importance of histologic study of the specimen.

The majority of these lesions were on or near the lesser curvature, which is the location of most gastric ulcers. The relatively frequent occurrence of massive bleeding and perforation shows that the size of the ulcer does not alter its susceptibility to the usual complications of ulcer disease.

While no characteristic clinical picture for large gastric ulcers has evolved from this study, one picture that does stand out is the disagreement with much that is currently accepted with regard to the incidence of carcinoma in the larger gastric *ulcers* (Fig. 7). In this series, even the largest ulcers—those with a diameter of 4.0 cm. or more—had only a 33 per cent incidence of carcinoma, in contrast to the commonly reported predominance of carcinoma in ulcers of this size.

It occurred to us that the deviation between the results reported here and those often found in the literature might be explained on the basis of the relatively small sample of patients studied. To clarify this point it was decided to review and tabulate the large gastric ulcers from articles which met the following criteria: 1. list ulcer size so that those lesions above 2.5 cm. could be selected, 2. provide a histologic report either from surgical or autopsy specimens to confirm the final diagnosis, and 3. include both benign and malignant disease

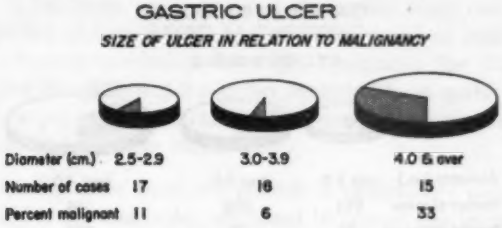

Fig. 7

unless the report was based on size alone and all ulcers reported happened to fall into one or the other category. When a diagnosis was based upon therapeutic response, as is common in the voluminous French literature dealing with giant gastric ulcers, such cases were not included in the final tabulation.

Using these basic criteria, it was possible to find 553 cases which could be evaluated on the basis of size (Table III). Since these cases come from clinics in all parts of the United States, Great Britain, and the European continent; from surgical files, autopsy files, and combinations of these, the problems of local bias and small-sample size must be eliminated and these figures must be given more consideration than the results obtained on the 48 patients studied in our own hospital. The close correlation between the two sets of figures, however, only serves to strengthen our figures.

Carcinoma is present in approximately one-third of the cases, regardless of whether one considers giant ulcers as those over 2.5 cm., those over 3.0 cm., or only those over 4.0 cm. (Fig. 8). It must be repeated that these figures deal only with those difficult diagnostic problems where one cannot be sure whether the *ulcer* is benign or malignant. The large, obvious carcinomas are not under con-

sideration. But among the true gastric ulcers of large size, a given lesion has a two to one chance of being benign.

Such a change in diagnostic probabilities requires certain changes in therapeutic outlook since the management of a potentially benign lesion must be quite different from that of a potentially malignant lesion. What then is the proper way to handle a large gastric ulcer?

The cases reviewed here show that medical treatment of a giant gastric ulcer is usually not effective. It would seem that an ulcer of this size, with its known poor response to therapy, and with the accepted difficulties in differential diagnosis, should not be subjected to any trial period of ulcer therapy. The long history that usually accompanies such disease is further reason not to delay definitive therapy. Even the most careful evaluation of the situation will often be unable to distinguish a benign from a malignant giant gastric ulcer. Thus,

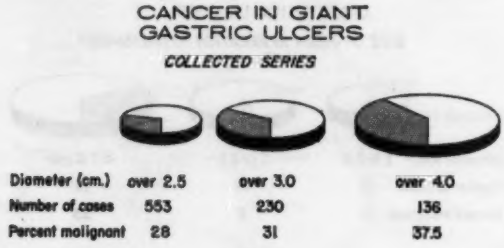

Fig. 8

even though benign disease is more common than malignant disease in giant ulcers, one should operate to alleviate symptoms and to obtain a histologic diagnosis.

The susceptibility of giant gastric ulcers to the usual complications of ulcer disease—perforation, massive bleeding, and pyloric obstruction—are further indications for early surgery.

If the internist, the gastroscopist, and the radiologist all have their difficulties in arriving at a correct diagnosis, the surgeon can also expect difficulty in making a correct diagnosis even with the ulcer under direct vision. The size of the ulcer, its adherence to, or invasion of, adjacent structures, the presence of enlarged local lymph nodes either as the result of inflammatory response or metastatic disease, and perhaps most important of all the old impression that these large ulcers must be malignant, will all combine to make a decision difficult even for the most experienced surgeon.

In the absence of some feature such as obvious metastases which would solve the dilemma, the following surgical plan would appear to be sound. After

the ulcer has been identified and its relation to other viscera determined, the next step should be a thorough careful exploration of the abdomen to determine whether distant metastases are present. If no metastases are found in the liver or elsewhere, then the stomach should be opened for more careful inspection of the ulcer.

Since the serosa over the ulcer may fail to give adequate hints as to the underlying pathology, and since adhesions to other organs may make adequate evaluation of the primary lesion difficult or impossible, it is desirable to open the stomach and directly visualize the ulcer. What may have been thought to be a large intraluminal lesion because of the massive reaction around it may be found to be only a giant ulcer. Direct visualization of the ulcer may show obvious areas of carcinoma, or may still leave the differential diagnosis undecided. Biopsy may be valuable, provided one remembers that the failure to find carcinoma in a single area does not completely eliminate carcinoma from the diagnosis. It has been suggested that the entire ulcer can be excised and given to the pathologist for study, but since he could at best do only frozen sections of the various quadrants, he might again miss the diagnosis. Granted that this will give the pathologist a better opportunity to make a diagnosis than would a single biopsy, it is not infallible, and under some circumstances it might be quite difficult to excise the entire ulcer.

If biopsy of the ulcer does not provide a satisfactory solution, and if enlarged lymph nodes are available, excisional biopsy of one or more of these for frozen section diagnosis may be helpful. The presence of frank carcinoma in the lymph node will simplify the diagnostic procedure, but the presence of inflammatory reaction only will not exclude the possibility of carcinoma being present in the ulcer.

Having completed these preliminary evaluations of the situation, the surgeon may still not be able to make a positive diagnosis, and may have to make a decision based upon inadequate information. The data provided in this study should now be of some use to him, as these data indicate that such a giant ulcer is more likely to be benign than malignant. We believe the ulcer should be treated on this basis. The multiple organ resections which have been undertaken in some of the cases reported here were certainly more than one would feel justified in doing for known benign disease, and should not be undertaken in the future in the absence of a definitive diagnosis. Superradical surgery is not desirable for benign disease. The mortality and morbidity of handling benign lesions should be reduced by this more conservative approach. If it is impossible to remove the entire base of the ulcer without removing other viscera, then thought should be given to leaving the base of the ulcer *in situ* with adequate resection of the remainder of the stomach, or perhaps with an exclusion procedure. If the lesion is a carcinoma and has already invaded other viscera, the chances of cure are significantly decreased, and the increased morbidity and

mortality of such an extensive procedure may well not be justified as a palliative procedure. On the other hand, if the lesion is benign, as it is likely to be on the basis of the figures reported here, then the patient will have been cured and simultaneously saved the necessity of an unduly debilitating operative procedure.

In the giant gastric ulcer where the presence or absence of malignant changes cannot be ascertained by any studies before or during surgery, then an adequate gastrectomy with removal of the greater omentum would be the procedure of choice. Removal of the spleen might also be considered depending upon the patient's condition, the accessibility of the spleen, and other factors to be determined in each individual case. Removal of portions of the pancreas, liver, or colon, and total gastrectomy do not seem justified for giant gastric ulcers.

Summary

Forty-eight gastric ulcers measuring over 2.5 cm. in diameter were recorded during an eight-year period at Charity Hospital. Forty of these lesions were benign.

Review of the literature revealed 553 gastric ulcers over 2.5 cm. in diameter, 72 per cent of which were benign.

Among the 136 collected cases over 4.0 cm. in diameter, only 37.5 per cent were malignant which compares closely with the 33 per cent incidence of malignancy in the cases of this same size from this series.

Large gastric ulcers have no characteristic clinical picture which will distinguish them from other gastric ulcers.

The difficulties in arriving at a correct diagnosis by clinical, x-ray, gastroscopic, and operative studies including gastrotomy for direct visualization of the ulcer emphasize the importance of making a correct diagnosis on the basis of histologic study only.

Perforation, massive bleeding, and pyloric obstruction occur with giant gastric ulcers just as with other gastric ulcers.

Large gastric ulcers do not respond to medical management.

Surgical management, with its more satisfactory results, should be the therapy of choice in large gastric ulcers.

Large gastric ulcers are most often benign.

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GASTRIC RESECTION*

Pathophysiology and Management of Certain Complications

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Jackson, Miss.

The complications which may follow the usually successful operation of partial gastric resection for peptic ulcer are many. Some of these occur immediately following surgery and are of concern particularly to the surgeon who has done the operation. Others occur at various intervals following operation, but are not peculiar to gastrectomy in that they may follow other operations as well.

The purpose here will be to examine the nature and to indicate the management of several types of postoperative gastric dysfunction which may require the best efforts of the surgeon, internist, and radiologist. The following conditions will be considered:

I. Infection

- a. Intraperitoneal abscesses due to spillage at surgery
- b. Blow-out of duodenal stump
- c. Leakage at gastrojejunal anastomosis

II. Proximal Loop Syndrome

- a. Regurgitation of bile
- b. Pain, epigastric fullness, and a palpable mass
- c. Perforation of duodenum due to gangrene
- d. Blow-out of duodenal stump

III. Gastric Retention

- a. Obstruction of distal stoma
- b. Jejunal adhesions
- c. Pancreatitis or other adjacent infection
- d. Neurogenic syndrome of distal loop
- e. Other rare complications such as internal herniation, intussusception of jejunum, and the suturing of the mesocolon to the jejunal loop instead of to the stomach in a posterior anastomosis

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IV. Nutritional Disturbances

a. The dumping syndrome and its variants (e.g. diarrhea)

b. Weight loss due to faulty digestion following extensive gastric resection

c. Gastroileal anastomosis (inadvertent)

d. Gastrojejunocolic fistula

V. Late Bleeding and Sepsis Due to Marginal Ulceration

The incidence with which the various complications listed occur is very difficult to determine. Occasionally surgeons do carefully report their complications, particularly late bleeding, but it has been our experience that a great many complications which follow gastric resection do not result in the death of the patient and hence can tend to be forgotten when the results are reported. Moreover, there are all degrees of the various types of complications to be considered, and it is a matter of the judgment or discretion of the individual surgeon as to whether a relatively minor example of this or that type of complication is included when the results of gastric resection are being reported. Therefore, no attempt will be made to offer figures for the precise incidence with which the various conditions occur. Nevertheless, some general indication of the prevalence of this or that complication will be offered in some instances. The particular purpose is, again, to emphasize the basic pathophysiology involved and the order in which the various complications have been listed has been determined more on the time sequence with which they may be anticipated than on the relative incidence or importance of the particular complication.

Intraperitoneal Infection Due to Spillage at Surgery

The incidence of serious infection following many operations has increased in recent years due to the increasing prevalence of antibiotic resistance of many organisms and, in particular, staphylococci. Thus, infection may be associated with gastric resection and certain types of this infection have constituted the commonest cause of death following this operation. Infection following a gastric resection may result from several major causes: First, spillage of bile from the duodenum in the process of dividing the stomach and closing the duodenal stump in the Billroth II operation. It represents a common source of peritoneal contamination. This spillage may also be aggravated by spillage at the time that the gastrojejunal anastomosis is performed. It has been our impression that many surgeons consider that the spillage of such material at operation is of little consequence, since the gastric juice and bile do have a relatively mild bacterial flora. On the other hand, if one should incur even one serious and fatal infection in 100 cases of gastric resection, the mortality would begin at 1 per cent regardless of what other fatal complications might ensue due to causes directly related to

the operation or to such catastrophic circumstances as hemiplegia, coronary thrombosis, or pulmonary embolus. It cannot be emphasized too strongly that, above all in the present relative ineffectiveness of antibiotics against certain bacterial organisms, absolutely every precaution must be taken against spillage of gastrointestinal contents at the operation. In the case of the duodenal closure this can be achieved by not opening the duodenal stump until it has been inverted, by careful packing of sponges around it as it is being closed, and by vigorous suction with the suction tip where necessary—all being used either alone or in combination as the occasion requires. It is realized that there are times when it is important to open the duodenum and directly to visualize the papilla of Vater, particularly when the ulcer is to be excised fairly far down in the duodenum. If by chance considerable spillage should occur in the course of the closure of the duodenal stump, we usually irrigate carefully in the right upper quadrant with saline solution in order to diminish the amount of bacterial contamination to the lowest point possible. Nevertheless, it is far preferable to avoid the contamination initially and this objective can usually be achieved with appropriate care.

Spillage during the course of performing the anastomosis is particularly prevalent and apparently is not a matter of concern to many. Nevertheless, if this results in abscess formation within the abdomen, the patient may from time to time lose his life. This spillage is somewhat more difficult to avoid than that incurred in the course of closing the duodenal stump, but it too can be minimized. First, gentle noncrushing clamps can be applied to the jejunum proximal and distal to the site at which the anastomosis is to be performed, the involved loop of jejunum then being carefully aspirated after the incision is made through its wall for the anastomosis. Moreover, great care can be employed in placing sponges around the stomach and jejunum that are being used for the anastomosis. It is not always as simple to prevent material from coming up from the stomach but, on the other hand, there is no continuous flow of juices as with the bile and pancreatic juice coming through the jejunum. If the stomach has been carefully emptied with the Levin tube preoperatively by overnight suction, particularly if this has been continued with an open Levin tube during the course of surgery up to the time that the anastomosis is to be performed, with suitable aspiration with the suction tip into the depths of the remaining gastric remnant, there should be no great volume of material remaining in the fundus to be forced up into the gastric lumen as the patient takes a deep breath or strains during the course of the anesthesia. Again, every precaution against contamination of the peritoneal cavity becomes increasingly essential as antibiotic resistance grows apace.

Blow-out of Duodenal Stump

Over the years one of the most serious sources of infection which proves fatal has been the blow-out or leakage at the duodenal stump. This will be con-

sidered somewhat further in examining complications of the proximal loop syndrome, but it is listed here because of its importance with respect to infection. Some surgeons consider this risk of infection and leakage at the duodenal stump sufficiently great that they drain all patients who have the Billroth II procedure with closure of the duodenal stump. Whereas, however, many surgeons do not routinely drain the duodenal stump area with drains in the subhepatic space, most do drain when there is any serious reason to feel that the closure of the duodenal stump has not been satisfactory due to technical imperfection or due to lack of healthy normal tissue with which to perform the inversion. Unfortunately, the duodenal stump may be closed quite satisfactorily but then be caused to leak because of an adhesion binding the proximal loop or because of obstruction of the proximal loop at the proximal stoma of the gastrojejunal anastomosis.

If leakage at the duodenal stump is recognized and promptly drained, converting the "internal" fistula with localized peritonitis into an external duodenal end fistula, most of these patients will survive. This is especially true because, since this is not a side fistula, as soon as the acute process of contamination and localized peritonitis in the right upper quadrant has begun to subside and a good drainage tract is established for the egress of the duodenal content, the patient can be fed by mouth or through the stomach into the distal jejunal loop and thus nutrition preserved over the days or weeks required for the duodenal fistula to close. Although the duodenal blow-out may have been the result of obstruction of the proximal stoma, this is most commonly due to edema with perhaps a degree of technical stenosis, and after a week or so the proximal loop usually drains satisfactorily. We shall have more to say about this subsequently.

Once again, however, failure to recognize the right upper quadrant pain, fever, perhaps shock, leucocytosis, and often an air fluid level in the right upper quadrant on roentgenography—failure to recognize these findings as probably being due to a blow-out of the duodenal stump and to drain promptly will often result in the loss of the patient. Of course, at times the infection will be walled off or contained by surrounding tissues, and the patient will survive the acute episode and may or may not require later operation for the drainage of the subhepatic or subdiaphragmatic abscess on the right side.

Leakage at Anastomosis

In our personal experience, leakage at the gastrojejunostomy closure or anastomosis is less common than is leakage at the duodenal stump. The reasons for the three cases which we remember were as follows: 1. Technical imperfection of inversion of the surfaces of the duodenum and stomach, recognized by the operator at the time of operation; 2. Abscess formation in the left upper quadrant immediately postoperatively, which doubtless contributed to the late leakage of the gastrojejunal anastomosis; 3. Hemorrhage into the peritoneal cavity following surgery, with a resulting infected hematoma which apparently

contributed to the leak of the anastomosis at about seven to ten days. In each of these three instances it was possible by means of roentgen studies with radiopaque media to identify the site of leakage as being at the gastrojejunal anastomosis. Two of these patients required operation and the third did not. All survived the episode. Contrasted with this relatively infrequent incidence of gastrojejunal anastomotic leakage, we have seen any number of patients who have leakage at the duodenal stump. Of these, the great majority have survived the episode with the prompt use of adequate surgical drainage, intravenous fluid maintenance, nasogastric suction for the first seven days, and then the employment of feeding by mouth in patients who had an end duodenal fistula, which was usually the case.

In the case of leakage from the duodenal stump or from the gastrojejunal anastomosis, the patient may become jaundiced due to leakage of bile into the free peritoneal cavity. Thus in any patient who becomes jaundiced in the postoperative period, particularly with abdominal pain, tenderness, rigidity, leucocytosis, and fever, one should immediately strongly consider the possibility of a leak at one of the two sites. Of course, there are other causes of jaundice—hepatitis, acute liver failure due to ligation of the hepatic artery and other causes, encroachment upon the common bile duct at one point or another, hemolysis, pancreatitis and, of course, gallstones.

Proximal Loop Syndrome

The proximal loop may be the site of origin of a variety of signs and symptoms, depending upon the pathology and the pathophysiology involved. First, the ulcer which may have been left in the duodenum at surgery may still give rise to pain, perforation, or bleeding. Lorber and Shay[2] studied the proximal loop in a number of patients by means of introducing a tube into the proximal loop through the stomach and visualizing this segment with barium study. They found that symptomatology arising in the proximal loop could be due to the retained ulcer, or to duodenitis. Of course, all are familiar with the secondary hemorrhage due to an ulcer which has been left in the duodenum, though this bleeding is not common even when ulcer has been left. Nevertheless, we believe that an ulcer should be removed wherever feasible. On the other hand, some ulcers are so situated and so far advanced with surrounding inflammation that it is the better part of wisdom to employ vagotomy-gastroenterostomy. Further, the most prominent symptom which has come to be associated with the "proximal loop syndrome" is that of the periodic regurgitation of a large volume of bile-stained material, followed by relief of the sense of fullness and distention and even pain which was previously present in the upper abdomen and in particular in the right upper quadrant. Not infrequently a mass is palpable prior to the emptying at periodic intervals of the proximal loop, but not always. This retention of bile and pancreatic juice in the proximal loop is due to partial obstruction of the proximal stoma or due to adhesions which are compressing

the proximal loop at various points. The regurgitation of bile with relief would not be so serious were it not for the even more sinister import of obstruction of the proximal stoma with distention of the proximal loop. The most severe complications which may arise from the obstruction of the proximal loop are, first, the blow-out of the duodenal stump as mentioned previously and, second, actual gangrene and perforation of the wall of the proximal loop at some point due to prolonged distention as might occur with any other distended loop of bowel eventually. We have seen gangrene and perforation in one patient who had previously had adhesions surrounding the proximal loop divided at a secondary operation. In this patient a hard mass was felt preoperatively before the second operation and at exploration this hard mass proved to be a tremendously distended proximal loop. The surgeon considered that by the lysis of adhesions he had achieved satisfactory decompression of the proximal loop but, unfortunately, this was not sufficient and about ten days later the patient was seized with excruciating pain in the upper abdomen and at operation he had gangrene of a considerable segment of the wall of the proximal jejunal loop and he subsequently died. The other patient had a large mass as visualized on soft tissue roentgenography and as visualized by the passage of barium into the proximal loop through a stenotic proximal stoma—a markedly distended proximal loop was disclosed. The patient was operated upon and a duodenojejunostomy was performed between the distended proximal loop and a loop of jejunum distal to the gastroenterostomy. This patient's obstruction was relieved and no further difficulty from this source was encountered. Thus, we feel that it is better to make certain of adequate decompression of the proximal loop by either taking down the gastroenterostomy or perhaps, better, by performing a duodenojejunostomy or an enteroenterostomy to by-pass any possible further obstruction of the proximal loop by stenosis at the proximal stoma.

In summary, proximal loop complications are due in most instances to a retained ulcer, to leakage at the duodenal stump, or to obstruction of the distal loop which of itself may contribute to either leakage at the duodenal stump, to imperfect emptying of the gastric remnant due to distortion by the distended proximal loop, or to actual gangrene of the wall of the proximal loop because of prolonged distention. The management of the condition may be either conservative with continued gastrointestinal suction until the edema subsides and the proximal loop is evacuating itself satisfactorily; or, one may need to operate upon the patient and lyse adhesions, or revise the proximal stoma, or anastomose the proximal loop to a loop of jejunum that is distal to the anastomosis to make certain that no further prolonged distention of the wall of the proximal loop will risk gangrene. Many surgeons prefer to introduce a Levin tube into the proximal loop at the close of gastric surgery to decompress this loop for a period of several days. In our experience, however, the tube has usually been removed before it is apparent that the proximal loop is not emptying satisfactorily. In fact, the greatest difficulty in managing proximal loop complications is the late

diagnosis of precisely what the difficulty is. This is especially the case when the patient is eating and retaining food.

Gastric Retention Postoperatively

Perhaps the complication that is most commonly associated with gastric resection in most surgeons' minds is that of retention by the gastric remnant following surgery; that is, failure of the gastric remnant to empty satisfactorily, with gastric retention and vomiting. This gives rise to the classic question of one surgeon to another to the effect: "How long do you wait?" Moreover, the causes for gastric retention constitute a source of great mystery to many physicians, largely because the different possible etiologic factors are not always analyzed critically. Actually, whereas most commonly it is thought that the obstruction is due to stenosis of the distal stoma by either technical imperfection at surgery or edema, there are a relatively large number of causes of failure of the residual gastric pouch to empty satisfactorily following gastric resection. Clearly, the precise cause of the obstruction, either functional or mechanical, may determine the type of management to be employed.

Obstruction of the Distal Stoma

Unquestionably the most frequent cause of retention following surgery, exclusive of proximal loop complications, is that of inadequate diameter of the distal stoma. This may be the result of an excessive invasion of tissue in the performance of the anastomosis at surgery, or it may be due to edematous swelling of the walls of the stomach and jejunum with consequent occlusion. Such gastric retention gives rise to a typical syndrome which is usually that of metabolic alkalosis due to the loss of chloride and to the loss of potassium. The patient may become considerably dehydrated; in addition he may lose salt which is not adequately replaced by glucose solutions. If nasogastric suction is not continued the patient may have enormous dilatation of the stomach. We have seen one patient who had retention of three liters of fluid, removed almost immediately by suction following obstruction at the distal stoma.

It is always a question of how long one should wait before exploring the patient following such obstruction. No definite time limit can be set but certainly one should wait at least two weeks and probably three weeks before a secondary operation is performed. Moreover, before a second operation is performed a careful roentgen study should be made with barium or lipiodol to determine whether obstruction of the distal stoma actually does exist, or whether the gastric dysfunction is in fact due to other causes. If the barium study shows that material does enter and pass on through the jejunum, it may identify other causes (below) that are resulting in poor emptying of the gastric remnant. If obstruction is demonstrated and by means of urecholine and prolonged nasogastric suction with intravenous fluids and blood transfusion it is not relieved,

eventually exploration will be required to revise the gastric stoma. To repeat, however, such a secondary operation for this particular cause is rarely required and conservatism is certainly to be practiced. For, in the vast majority of instances there is perhaps an element of technical stenosis at the anastomosis, but certainly a large portion of the stenosis is due to edema and this will eventually subside in most patients. Again, the patient must be adequately supported with intravenous fluids that contain enough salt and potassium and with blood transfusion where indicated. The performance of a jejunostomy for feeding purposes has not usually been required, in our experience, and we rarely resort to it.

Jejunal Adhesions

Jejunal adhesions do constitute a fairly common source of poor gastric emptying following gastric resection. This is a particularly deceptive circumstance in that the obstruction may not be complete on barium study, but it is sufficiently severe to result in partial chronic low-grade obstruction with a degree of gastric retention and with chronic inanition. The patient may eat and retain a portion of the ingested food, vomiting a portion of it as well. Barium study may reveal that material does pass down the jejunum but, if at last operation must be performed, it will be found that partial small bowel obstruction is present. Such patients may take and retain enough liquid to avoid severe dehydration but not enough nutrient to avoid inanition. If the barium study reveals that material does pass out of the stomach promptly, but the patient continues to go slowly down hill with incipient starvation, we are apt to explore the abdomen.

Neurogenic Syndrome of Distal Loop

In certain patients there develops a neuromuscular defect of the distal loop which has been termed the "neurogenic syndrome of the distal loop". In essence, this appears to be due to the incision of the jejunum for the performance of the anastomosis. It has been found by Golden[1] to be more prevalent after the Polya type of anastomosis in the Billroth II operation than following the Hofmeister modification of this procedure. Essentially, Golden studied the distal loop in patients who had poor gastric emptying and found that, whereas there was no mechanical obstruction in this loop, there was an absence of normal peristaltic activity. These patients developed gastric retention beginning about the fifth to the seventh day, after they had previously been emptying their gastric pouches, and this persisted from one to two or even three weeks. In all instances, however, the function did return to the distal loop and the patient eventually recovered.

Thus, this possibility is to be considered where it can be demonstrated that barium can be manually expressed from the gastric pouch and into the small bowel without apparent obstruction. Fluoroscopy would be required to identify the absence of peristalsis in the distal loop.

Pancreatitis or Other Adjacent Inflammation

In the presence of acute pancreatitis or other surrounding infection the gastric remnant may be distorted in such a manner as to preclude satisfactory emptying. Of course, the anastomosis is quite close to the pancreas when it is performed behind the colon, and we have frequently seen obstruction at the ligament of Treitz in pancreatitis due to other circumstances.

The pancreatitis is to be managed conservatively unless abscesses form and must be drained, and the other surrounding infection will be managed as described previously.

Jejunal Obstruction Due to the Suturing of the Mesocolon to the Jejunal Loop Instead of to the Stomach in a Posterior Anastomosis

It is not always appreciated that the mesentery of the transverse colon should be sutured to the more rigid wall of the stomach in the course of performing a posterior anastomosis, rather than to the more pliable jejunum. In the occasional patient this technical defect will result in retention. The reason for this is that the jejunum is readily collapsible. Unfortunately, this circumstance is not readily diagnosed, even by the radiologist. This is due to the fact that the barium may pass fairly readily into the distal loop, particularly with manual pressure on the part of the radiologist at fluoroscopy. Thus, no definite site of obstruction is seen. Moreover, the patient may ingest sufficient fluid to avoid dehydration, but the nutritive intake is not sufficient to avoid progressive weight loss. Only if it can be determined that the mesocolon was sutured to the stomach or to the jejunum can the possibility that this defect is the cause of the gastric retention be established with reasonable certainty. If the patient comes from another institution where the information is not available, exploration is occasionally justified if all other measures to improve or await gastric emptying have been exhausted. Following the simple advancement of the mesocolon onto the wall of the stomach after removing it from the jejunum, the patient may promptly gain 10 to 15 pounds in weight.

Internal Herniation and Intussusception

The complications of internal herniation, particularly following an anterior anastomosis in the Billroth II operation, and of intussusception of the upper jejunum are not common. Nevertheless, they do occur and should be considered. The diagnosis of internal herniation would be essentially that of intestinal obstruction which would require surgery for the correction of intestinal obstruction with the usual signs and symptoms thereof. Intussusception may occur without obvious cause, but it has occasionally followed the withdrawal of a tube, usually a Miller-Abbott tube. As a rule one would not be using a Miller-Abbott tube in a patient who had had a gastric resection, but occasionally such tubes are passed into the distal loop either for decompression or for feeding a

patient who has, for example, a duodenal end fistula. We have seen intussusception which required operation in two patients. In both instances the radiologist was able to diagnose only that mechanical intestinal obstruction existed. It was not until the abdomen had been opened that the intussuscepted jejunum was identified. The jejunum may intussuscept into the stomach.

Nutritional Disturbances

Of all the complications of gastric resection, those which involve nutritional disturbances are perhaps of the greatest interest to the internist, particularly as up to the point that they begin to appear the patient has been largely under the supervision of the surgeon. Gastric resection frequently does improve the nutritional management of a patient, in that the pain associated with the condition is usually relieved. On the other hand, many patients constitute even more severe nutritive problems postoperatively, largely because the regulatory action of the pyloric sphincter has been lost or, because the food no longer passes through the normal enzymatic digestive mixing of the duodenum in the Billroth II operation. As a general rule, the more stomach removed the greater the postoperative nutritional disturbances.

The Dumping Syndrome and Its Variants

The constellation of symptoms that have come to be collectively termed "the dumping syndrome" are experienced by some 10 to 40 per cent of patients who have gastric resection, depending upon the extent of the resection performed and upon the clinic reporting its results. Moreover, one patient may not be disturbed by symptomatology which would be considered largely incapacitating by another, with the consequent omission of the first patient from the listing and the inclusion of the second. In any event, following a high gastric resection, or the vagotomy-gastroenterostomy procedure, one may anticipate the development of dumping symptoms in approximately 25 per cent of the patients. Such symptoms follow a meal and, in particular, a fairly large meal in the course of which a liberal amount of fluid is taken. The symptoms consist variously of cramps, nausea, sweating, dizziness, rapid pulse, and upon occasion vomiting and later diarrhea. The patient often feels so weak that he must lie down to avoid fainting. The symptomatology usually subsides over the course of an hour. This is repeated with the next meal. In time the patient learns that it is caused by food and often tends to lose weight because he is afraid of producing the symptoms by eating. It has been found that the restriction of fluid intake with the meal (fluids being consumed between meals) lessens the symptomatology. In some patients diarrhea may follow promptly the ingestion of food and these patients may not experience the other symptoms listed above. Moreover, the patient may have a severe dumping syndrome without diarrhea for a number of months only to have diarrhea develop with a remission of the symptoms of dumping otherwise.

Various studies have been devoted to an elucidation of precisely what the pathophysiology is which causes the symptoms referred to collectively as the dumping syndrome. At first it was thought that the hypocalcemia which was observed in the course of the attack was the cause of the symptomatology. More recently, however, perhaps the majority of physicians have come to accept the hypovolemic explanation of the phenomenon. In brief, the regulatory action of the pylorus has been lost, and food materials are no longer rendered isotonic in the stomach prior to their release into the duodenum or jejunum, as the case may be. Thus, in all procedures—Billroth I, Billroth II, or vagotomy-gastroenterostomy—the hypertonic material passes abruptly from the remaining stomach into the jejunum.

In *clinical experiments* it has been found that the symptomatology of the dumping syndrome can be reproduced by inserting into the jejunum a concentrated solution of sucrose or of magnesium sulfate. This would argue strongly in favor of the idea that an increased volume of fluid is being drawn into the lumen of the bowel from the bowel wall by virtue of the hypertonic solution instilled into the lumen of the gut. In further clinical studies, Randall and his associates[4] found that the plasma volume of the individual might be diminished by even as much as one liter during the acute symptoms of the dumping syndrome. Such blood volume changes have also been found by others. All in all, we feel that the evidence favors this fluid loss into the bowel lumen as the primary factor in the symptomatology which accompanies the dumping syndrome.

The *management of the dumping syndrome* is not always satisfactory, but a number of measures have been found to be useful. First, as indicated previously, the patient should be encouraged not to take a large amount of liquid with the meal, but to consume water between meals. Second, it is far better for these individuals to eat six or eight small meals each day rather than to try to eat only three larger meals per day. Third, the patient should be encouraged to realize that the acute symptoms of the dumping syndrome gradually subside to minimal symptomatology in most subjects. That is, the dumping syndrome does not persist permanently in most patients who have this discomfort following gastric resection. Fourth, if diarrhea constitutes a major factor in the dumping syndrome, during the early period following resection, the use of paregoric, Banthine-like drugs, and kaopectate may diminish the caloric, fat, and nitrogen loss in the stools due to this intestinal dysfunction. Fifth, there is considerable evidence that the Hofmeister type of Billroth II operation may be accompanied by less incidence of the dumping syndrome than the Polya operation. Sixth, in some patients who continue to have severe dumping, the conversion of a Billroth II anastomosis to a Billroth I anastomosis has diminished the severity and other nutritional disturbances. Nevertheless, this alternative should not be resorted to until conservative measures and time have been given adequate opportunity to achieve a satisfactory result.

Weight Loss Due to Faulty Digestion Following Extensive Gastric Resection

An intractable weight loss or inability of very lean subjects to regain weight following gastric resection can be a most distressing situation, particularly in women. If the patient is in his usual or normal state of nutrition, whatever this may be, most subjects will lose some additional weight following a liberal gastric resection of, say, 75 per cent. The reasons for this have been mentioned above. On the other hand, if the individual was chronically ill with a severe peptic ulcer, he may regain considerable weight when the pain and other symptomatology have been relieved by a successful removal of the ulceration. Nevertheless, it should be borne in mind that the weight curve generally tends to go downward and level off at a lower value than was present in the normal subject. Therefore, whereas a 75 per cent gastric resection in the obese may result in an average sized individual and a similar resection result in a lean person when the subject was of average obesity preoperatively, the removal of this amount of stomach in the patient who is already lean may result in a virtually emaciated individual. Thus, as has been pointed out by Zollinger[5] and his associates, it is advisable to revise the extent of resection downward as the subjects exhibit increasing degrees of leanness. Whereas a liberal Billroth II resection may be performed in the obese and average sized individuals, a Billroth I or a vagotomy-pyloroplasty or vagotomy-gastroenterostomy should probably be employed in the lean individual to avoid a person who is excessively lean in the late postoperative period.

It was found by Perman[3] that the conversion of a Billroth II anastomosis to a Billroth I anastomosis resulted in the gaining of considerable weight by certain subjects who had become emaciated following gastric resection. Moreover, it has been found that the loss of calories and nitrogen in the stools is less following a Billroth I operation or vagotomy-gastroenterostomy than following a liberal (75 per cent) Billroth II operation.

In summary, the habitus of the subject, as well as the severity of the ulcer diathesis, must both be borne in mind in choosing the operation to be employed for the individual patient.

Gastroileal Anastomosis (Inadvertent)

In the occasional patient the surgeon will have mistakenly anastomosed the stomach to the ileum in performing the gastroenterostomy. This contingency should always be considered when the patient has loose stools and diarrhea when bowel movements begin immediately following surgery. This is, of course, due to the fact that the food material passes directly from the stomach into the terminal ileum and into the colon. There is insufficient absorptive surface for water and other nutrients, or for digestive enzymes to achieve the usual degree of digestion to permit absorption. If this condition is but thought of it is readily

diagnosed by a gastrointestinal barium study which demonstrates the anastomosis of the stomach to terminal ileum. It is of course easily repaired surgically. Nevertheless, many patients with this condition have not been diagnosed until an advanced state of starvation had occurred.

Gastrojejunocolic Fistula

The gastrojejunocolic fistula has been alluded to previously, but it is included here because it is one of the most serious causes of nutritional deficiency following gastric resection. The condition develops when marginal ulceration extends through the wall of the jejunum into the colon. This complication is more common following an anterior anastomosis than following a posterior anastomosis, but, upon occasion, it may occur with a posterior anastomosis as well. In this condition the patient has loose stools in that the material eaten passes directly from the stomach into the colon and may be passed by rectum in the same state in which it was ingested. Naturally, since the greater part of the absorptive surface of the bowel may thus be shortcircuited—particularly when the communication between the stomach and colon is large—the patient may lose weight and very shortly be in the most serious circumstances due to starvation and, usually, infection surrounding the ulceration. Not only is the food the patient eats lost, but the offensive odor of the regurgitation of colonic content into the stomach with fecal vomiting may impair the appetite so that the patient consumes hardly anything.

The *diagnosis* of the gastrojejunocolic fistula is made largely on the basis of the signs and symptoms of marginal ulceration, the passage of food materials virtually unchanged and the demonstration of the gastrocolic communication by the roentgenologist on barium study.

The *management* of gastrojejunocolic fistula consists of achieving the best nutrition and replacement of blood volume possible and then operating for correction of the defect. More and more, the tendency has been to excise the involved portions of jejunum, stomach and colon, reestablish continuity of jejunum and colon and then to perform a new gastrojejunostomy at a different site. As a rule, the operation is successful. Nevertheless, these patients are usually in very serious condition, if the communication is a large one and has been long-standing, and any major operation in patients in this defect carries with it a definite mortality rate.

Hemorrhage Due to Recurrent Ulceration

It was indicated above that marginal ulceration may result in penetration or perforation of the ulcer with surrounding sepsis or with the formation of a gastrojejunocolic fistula. Of course, the more common complication following the development of a marginal ulcer with the usual ulcer symptoms (though these may be at times more prominent in the back) is that of bleeding from the

recurrent ulceration either at the gastroenterostomy or, in the case of the Billroth I procedure, in the duodenum. The incidence with which this complication of marginal or recurrent ulceration develops, and the incidence with which hemorrhage occurs, are dependent upon a number of factors. First, the more liberal the gastric resection, the less the incidence of late recurrence of ulceration. On the other hand, as noted above, the more liberal the resection, the greater the incidence of postoperative nutritional disturbances. Second, the more active the ulcer diathesis in the individual in the beginning, the more likely is there to be ulcer recurrence. In other words, the patient with a markedly elevated gastric activity and a strong constitutional predisposition to emotional tension which begets peptic ulceration in the susceptible individual, is likely to be associated with a greater incidence of ulcer recurrence. Third, the presence of associated endocrine abnormalities—including the ulcerogenic tumor of the pancreas, the intracranial pituitary lesion, or the hyperactivity of a parathyroid adenoma—any of these may be associated with a relatively intractable ulcer diathesis.

Nevertheless, all in all, the incidence of marginal ulceration following the liberal Billroth II operation of approximately 75 per cent ranges between 3 and 5 per cent. While figures are not as readily available concerning the incidence of ulceration following the Billroth I operation, it is likely that the incidence of recurrent duodenal ulceration is in the neighborhood of from 3 to 5 per cent also. The vagotomy-gastroenterostomy data are also difficult to evaluate, but it appears likely that the incidence of recurrent or marginal ulceration following vagotomy-gastroenterostomy may be slightly higher than that following a liberal or 75 per cent Billroth II gastric resection.

The *management of marginal ulceration* resolves itself into several approaches. First, the patient may be treated intensively with medical measures of the usual variety. Second, if necessary one can perform a bilateral vagotomy through the chest, that is, above the diaphragm. Third, if this second procedure does not prove adequate to control the ulcer diathesis in the given individual, a second laparotomy may be required and at this time further stomach can be resected. Unfortunately, this may result in definite nutritional disturbances over and above those present previously.

Summary and Conclusions

1. Several broad groups of complications which may follow gastric resection have been discussed. Among these are infection, the proximal loop syndrome, gastric retention due to numerous causes, nutritional disturbances and late bleeding due to marginal ulceration.

2. Infection now constitutes a major hazard following gastric resection, particularly in view of the increasing antibiotic resistance of staphylococci and certain other organisms. The intraperitoneal infections which may develop due

to spillage at operation, a blow-out of the duodenal stump, or a leakage at the gastrojejunal anastomosis account for the major source of the mortality associated with gastric resection. When antibiotics are used these collections of pus may assume an indolent character which results in long delayed diagnosis and drainage often comes at a time when the patient's physiologic reserves have been depleted to a point that surgery for drainage is hazardous indeed.

3. The proximal loop syndrome may consist largely of the periodic regurgitation of large amounts of bile-stained material or it may result in either a blow-out of the duodenal stump or in gangrene of the wall of the proximal loop with peritonitis. This condition, which is due to obstruction of the proximal loop by adhesions or by edema or technical imperfection at the proximal stoma, must be recognized early if severe, even fatal, complications due to this contingency are to be avoided.

4. Gastric retention following gastric surgery may be due to a variety of causes. Among these are: obstruction of the distal stoma, the neurogenic syndrome of the distal loop, pancreatitis and other infection, internal herniation, intussusception of the jejunum, and the suturing of the mesocolon to the jejunal loop instead of to the stomach in a posterior anastomosis. Most patients with poor gastric emptying following gastric resection can be managed expectantly and conservative measures usually suffice, though several weeks may elapse before completely satisfactory gastric emptying has been achieved.

5. Nutritional disturbances following gastric resection may be due to the dumping syndrome and variants thereof, to weight loss due to faulty digestion, to an inadvertent gastroileal anastomosis, or to a gastrojejunocolic fistula. The measures to be employed in the management of intractable nutritional deficit following gastric resection are dependent upon the identification of the cause of the intractable malnutrition.

6. Hemorrhage due to marginal ulceration constitutes one of the most common complications following gastric resection. The incidence of the complication is probably approximately the same for the Billroth II and the Billroth I operations, and it may be slightly greater following vagotomy-gastroenterostomy. If conservative measures are not adequate when such recurrent ulceration occurs, the addition of a vagotomy should be considered in patients who had the Billroth I or the Billroth II operation. If the additional vagotomy does not control the ulcer diathesis in the given patient following the Billroth I or the Billroth II operation, or if the patient with vagotomy-gastroenterostomy cannot be managed satisfactorily conservatively, then additional stomach must be removed.

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RESULTS OF SUBTOTAL GASTRECTOMY IN 449 PATIENTS WITH BENIGN PEPTIC ULCERS*

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Periodic evaluation of the surgical treatment of benign peptic ulcer is necessary in order to extend or restrict indications for operation and possibly to modify existing technics. The present study is based on experience with this condition at the Ochsner Clinic during the years from 1942 through 1956. More recent cases were excluded because the period of postoperative observation is insufficient for evaluation of results. We have used as a guide for evaluation of results the report of the Committee on Surgical Procedures of the National Committee on Peptic Ulcers of the American Gastroenterological Association[1].

Material

During the period of this study 462 patients were operated on for benign peptic ulcer of the duodenum or stomach; included are 314 duodenal, 123 gastric and 25 gastrojejunal ulcers. Of these, 449 had subtotal gastrectomies. Adequate follow-up data were obtained in 413 patients (92 per cent).

Indications

Indications for operation were those generally accepted. For duodenal ulcer the various complications and unsuccessful results of medical treatment were considered sufficient reasons for operation whereas gastric ulcers must always be suspected to be malignant unless proved otherwise. For these reasons, only 12 per cent of the patients (314 of 2,587) with a diagnosis of duodenal ulcer in our Clinic were operated upon whereas the percentage of patients with gastric ulcers was 40 (123 of 302 patients).

Special Characteristics of Patients

One should not lose sight of the fact that the patient who is operated on for a peptic ulcer generally falls in a special group. Reference has already been made to the operative indications, and it appears that in general, complications resulting from a high ulcer tendency and intractability determine the duodenal group, and failure to heal, the gastric group. It was also noted that approxi-

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mately 20 per cent of the patients treated surgically at the Ochsner Clinic had had previous operations for ulcer, and although many of the operative procedures were inadequate, this fact is some indication that these patients form a group whose tendency to development of ulcers is high. In 9 per cent a perforation was closed, 8 per cent had gastroenterostomy and 2 per cent other operations. These considerations seem to justify the contention that the patient who requires operation for peptic ulcer is, for one reason or another, a person with an especially great tendency to ulceration.

It is of interest that the group under study is a rather homogeneous one because, although the operations were performed by several surgeons, almost

TABLE I

SURGICAL TREATMENT OF BENIGN PEPTIC ULCER IN 462 PATIENTS*
(JAN. 1942 TO JAN. 1957)

Type		Cases
Billroth I		3
Billroth II		444
Polya anterior	1	
Polya posterior	17	
Hofmeister anterior	13	
Hofmeister posterior	413	
Total gastrectomy		3
Segmental resection		3
Gastroenterostomy		2
Closure of perforation		3
Vagotomy		27
alone	1	
with gastroenterostomy	1	
with subtotal gastrectomy	25	

*Some patients had more than one operation.

all patients had a posterior Hofmeister modification of the Billroth II, with removal of 75 per cent of the stomach or more. Other operations were the exception (Table I).

OPERATIVE MORTALITY RATE

The immediate danger of operation has become minimal. The total postoperative mortality rate was 1.8 per cent, with only slight difference when 80 per cent or more of the stomach was removed as when more conservative resection was done (Table II). Also, 10 per cent of these patients were bleeding at the time of operation or had bled during the previous few days. Inasmuch

as leakage from the duodenal stump or anastomotic site accounted for about one-half the deaths, there is reason to believe the danger from gastrectomy can be reduced still further. The postoperative mortality rate was only slightly higher in our patients with gastric ulcer.

Grading of Results

Evaluation of the patient's postoperative condition is far from being exact. This is particularly true when the criteria are subjective symptoms; hence, every effort has been made to grade the results in the strictest manner. We have attempted to correlate the amount of stomach removed with the result; hence, we have labelled the gastrectomy radical if 80 per cent or more of the stomach was removed and conservative if less than this was excised. Seventy-six per cent of our cases fell in the former group.

TABLE II

Operative Mortality Rate* of 449 Subtotal Gastrectomies

Type	Radical		Conservative		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
Duodenal	229	3	79	2	308	5
Gastric	95	3	22	0	117	3
Gastrojejunal	19	0	5	0	24	0
Total	343	6 (1.7%)	106	2 (1.9%)	449	8 (1.8%)

*Includes patients bleeding at the time of operation.

Complications of Operation

One of the most definite sequels to gastrectomy is gastrojejunal ulcer. Some maintain that it is better to leave more stomach for the patient's comfort, even though this entails some added risk of subsequent ulceration. Our experience indicates that slightly more remaining stomach does create such a hazard. Thus, gastrojejunal ulcer developed in only 1.3 per cent of patients who had radical operation as compared with 10 per cent of those having conservative resection. In agreement with others we noted that this sequel rarely follows gastrectomy for gastric ulcer, developing in only one patient in our series. The incidence of gastrojejunal ulcer in 413 gastrectomies was 3.4 per cent (Table III). These statistics substantiate the observations of others that the incidence of this complication is in direct relation to the amount of stomach removed.

The "dumping" syndrome after gastric resection occurs commonly. It occurred in one-third of our patients but in most instances it was mild and of

short duration. Only about 6 per cent of cases were classified as moderate and another 2½ per cent as severe (Table IV). The amount of stomach removed seems to have no influence on the incidence of this common sequel. Some patients complain of other types of postprandial discomfort. Sometimes this is due to overeating but in most instances it should be classified as an atypical dumping syndrome.

Inability to maintain or gain weight is another complaint of many patients. There appears to be a definite correlation between loss of weight and the amount of stomach removed, for in the radical group 37 per cent lost significant weight, whereas in the conservative group only 31 per cent lost weight. Then, too, the average weight lost was greater when more stomach was removed (20 lbs. and 18 lbs., respectively). There seems to be an individual difference in patients as

TABLE III

INCIDENCE OF GASTROJEJUNAL ULCER AFTER SUBTOTAL GASTRECTOMY IN 413 PATIENTS

Type	Cases	Ulcers	%
Radical	317	4	1.3
Conservative	96	10	10.4
Total	413	14	3.4

to how much stomach can be removed without loss of weight, but once this amount is exceeded, each increment brings about more disturbance in nutrition.

RESULTS

Many have evaluated results of gastric resection. Despite sincere attempts to standardize interpretations, these must necessarily vary and in the end reflect many individual conceptions. We have attempted to apply the strictest standards as objectively as possible in our study. The results in general proved satisfactory when judged by several criteria: significant loss of weight, dumping syndrome and diarrhea in addition to: 1. roentgenographic evidence of ulcer, 2. hemorrhage, 3. patient satisfaction, 4. inability to work and 5. symptoms of ulcer.

If any of these were present in significant degree, the result was classified as unsatisfactory. On this basis a satisfactory result was obtained in 90 per cent of the entire group and the remaining 10 per cent were thought to be unsatisfactory. Removal of 80 per cent of the stomach gave better end results than more conservative surgical procedures. The unsatisfactory results in the two groups are 8.5 per cent and 18.7 per cent, respectively (Table V). This difference was much greater than was anticipated, and in our opinion, constitutes the

most significant finding of this study. It should be pointed out that in a previous study we[2] were unable to demonstrate any significant difference in the incidence of dumping syndrome or postprandial pain between these two groups. This, then, makes a good case for radical rather than conservative resection.

We have seldom employed vagotomy in the treatment of benign peptic ulcer. In our series only 25 patients had vagotomy at the time of subtotal gastrectomy. We have been unable to locate 2 of these patients for postoperative evaluation, but among the remaining 23, satisfactory results were obtained in 21 (91 per cent). One of the 2 patients with poor results had severe dumping syndrome, and the other severe loss of weight. In none of the 23 patients, however, did gastrojejunal ulcer develop, although 12 patients had only moderate resection of the stomach. Whereas this is too small a group from which to draw adequate conclusions, in our limited experience results of vagotomy in association with subtotal gastrectomy were no better than results of subtotal gastrectomy alone. Vagotomy, however, did seem to offer protection from later development of gastrojejunal ulcer to patients who had only moderate subtotal resection.

TABLE IV

INCIDENCE OF DUMPING SYNDROME AFTER SUBTOTAL GASTRECTOMY IN 413 PATIENTS

	Radical (317 Patients)		Conservative (96 Patients)	
Severity	Cases	%	Cases	%
Mild	76	24	24	25
Moderate	23	7	5	5
Severe	6	2	3	3
Total	105	33	32	33

TABLE V

RESULTS OF 413 CASES OF SUBTOTAL GASTRECTOMY

	Results			
	Satisfactory		Unsatisfactory	
Type	Cases	%	Cases	%
Radical	378	91.5	35	8.5
Conservative	336	81.3	77	18.7

There appeared to be a significant relation between the patient's sex and the final results. Although a greater percentage of male patients with benign peptic ulcer are treated surgically (and this could be assumed to indicate that this disease is more severe in them), results of subtotal gastrectomy are much better in the male patient. This is true whether the surgical procedure is conservative or radical (Table VI).

Conclusions

The results of a study of 449 gastrectomies for benign peptic ulcer were generally satisfactory. These represented 12 per cent of the duodenal ulcers seen during the same period and 40 per cent of the gastric ulcers. Satisfactory results

TABLE VI

Relation of Sex to Final Result in 413 Cases of Subtotal Gastrectomy

Sex	Procedure	Results				Total Cases
		Satisfactory		Unsatisfactory		
		Cases	%	Cases	%	
Male	Radical	245	94.2	15	5.8	260
	Conservative	70	85.4	12	14.6	82
	Total					342
Female	Radical	47	82.5	10	17.5	57
	Conservative	10	71.4	4	28.6	14
	Total					71

were obtained in 90 per cent. Results of radical gastrectomy were better in the end than those of more conservative resection. The operative mortality rate was 1.8 per cent and the incidence of recurrent ulceration 3.4 per cent.

Subtotal gastrectomy, when correctly performed, has proved to be a satisfactory operation in our experience, despite the fact that the patients are a selected group with a high tendency to peptic ulceration. Modified technics of treatment must demonstrate their superiority before subtotal gastrectomy is discarded.

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Discussion

Dr. O. H. Wangensteen:—I think we have heard three very interesting, straightforward, conservative papers. The paper of Dr. Cohn should do a great deal to clear the atmosphere in a very controversial question. He appears to have carried his case, viz., that cancer has a definite relatedness to the problem of gastric ulcer. There are a few gastroenterologists, and roentgenologists too for that matter, who feel they possess an almost infallible, celestial intuition in their ability to tell which gastric defect is benign.

A number of physicians believe that surgeons are too knife-happy in the presence of a gastric defect which may prove to be either cancer or ulcer. In the light of the figures, which Dr. Cohn has shown us, physicians as well as surgeons would be well advised to suggest that surgery be invoked early to resolve the dilemma. It is too much to ask of patients with large gastric defects that they accept a 25 to 33 per cent risk of having a cancer by a "wait and see policy", when ready resolution of the problem can be accomplished by timely surgery.

More patients die of gastric ulcer than of duodenal ulcer. One reason I suspect is that some of them have gastric cancer. Certainly there is a so-called "garden variety" of gastric ulcer near the infundibulum on the lesser curvature which roentgenologists, generally, are more successful in differentiating with reference to the question of benignancy or malignancy. In his discussion of the problem, Dr. Cohn more likely was referring particularly to the "hot house variety" of gastric ulcer—a more select group.

We need always to be particularly vigilant over these cases, bearing in mind that any patient with a persistent gastric defect, may be harboring a cancer. I have learned that my simple role as a gastric consultant is to ask the patient under scrutiny whether his stomach has been pumped. Certainly the patient who is achlorhydric with a persistent gastric defect—that patient most certainly needs a gastric resection. In my experience, such lesions invariably are cancer. The strange thing is that this happens so frequently. The patient has been gastroscoped several times and has had innumerable x-rays, but no one has determined the gastric acidity. This is an occurrence that happens in my community even amongst the internists and gastroenterologists, who one might reasonably expect to know better. Gastric aspiration must not be discarded.

Dr. Hardy obviously has seen the entire gamut of complications that can attend a Billroth II resection. I assume it would be proper to suggest that anyone who has done a fair number of these operations, similarly, has had some of the experiences that Dr. Hardy enumerated. I rarely do the Billroth operation for ulcer—only for an antral ulcer. For gastric ulcer proximal to the antrum, which are definitely not cancer and for all duodenal ulcers, I prefer segmental gastric resection.

My first segmental gastric resections were done between six and ten years ago—the first in 1949. My colleague, Dr. Donald J. Ferguson, has done almost 400 cases and we at the University Hospital have almost 300. In recent years, I have been doing a 50 per cent segmental resection. In this group, there have been no recurrent ulcers.

Following the extended segmental, which I did in the beginning, there have been no recurrences. Because dumping was frequent, I reverted to a smaller resection. A 25 per cent segmental is too small. In that group, I have had two recurrences.

Any surgeon who adopts segmental operation in very difficult duodenal ulcers will find that many of his prior technical difficulties with the Billroth II operation have been resolved.

Ferguson does a pylorotomy only in the presence of obstruction at the pylorus for he takes pains to preserve the vagal innervation to the pylorus by elevating the structures along the lesser curvature. I have modified the conventional Heineke-Mikulicz pylorotomy by elevating the anterior wall at the pylorus with an Allis clamp. I then make a short transverse cut with a scissors, slicing away a small ellipse which opens the mucosa. This small opening is then enlarged at its middle by a short slit in the axis of the bowel on both sides of the ellipse. In this manner, in the closure, the usual "dog ears" of the Heineke-Mikulicz pylorotomy are avoided. It is a very simple thing to perform the pyloroplasty by this method. If an ulcer crater is present in the duodenum, one sutures the adjacent edges of the mucosa over the crater [*Postgraduate Medicine* 23:466 (May), 1958].

We have had an experience during the past year in the control of massive gastric hemorrhage which has been very illuminating. To William Beaumont, pioneer army surgeon, we owe much of our knowledge of gastric secretion. William Beaumont, however, failed to note the presence of pepsin in the stomach. Beaumont has come to be known as the Apostle of American Physiology, and rightly so. It remained for Schwann in Johannes Müller's laboratory to ascertain the presence of a peptic ferment in the gastric juice. Beaumont's own observations, however, suggested very definitely the presence of an agency in the gastric juice, beyond HCl responsible for digestion.

The esophagus of the intact cat has been used in our clinic over a number of years to ascertain the digestive power of gastric juice. When the cat, into whose esophagus the overnight gastric aspirations obtained are dripped, from a patient with duodenal ulcer, is kept cool and the juice too (18-20° C)—such juice, which would perforate the cat's esophagus under normothermic conditions within two hours, does no harm to the cool cat's esophagus.

We obtained some of your big Louisiana bullfrogs. I believe you call them *Rana catesbiana*. We put one of our small Minnesota spring frogs, *Rana pipiens*,

into the big frog's stomach. When retrieved in six hours sojourn in the warm frog's stomach, the little frog was scarcely identifiable; but even after 24 hours in the big cool frog, the little frog was still alive. By attaching a small polyethylene tube to the nose of the *Rana pipiens*, the little frog when placed in the stomach of a dog kept at 4° C by local gastric hypothermia—the little frog, under these conditions, is alive at 36 hours and survives! The frog in the warm stomach of another dog is scarcely identifiable after four hours. We have now treated 16 patients with massive gastric hemorrhage with local gastric cooling (25 at time of writing, 24 February 1959). A small balloon is passed down having a small inflow catheter and a larger outflow tube; both catheters are incorporated into one. A large silastic No. 18 French tube is far better tolerated by the patient than conventional large tubes; moreover, it can be withdrawn through the nose. Remarkably too, patients with portal hypertension appear to respond about as well to gastric cooling as do patients having massive hemorrhage from a duodenal ulcer. It is going to take a larger experience to define more precisely the advantages and shortcomings of the method but it does appear to be a therapeutic agent of real promise. My associates, Drs. H. D. Root, P. A. Salmon, and W. O. Griffen, have given these studies helpful impetus in the laboratory [*Surgery* 44:265 (Aug.), 1958]. It would appear there are three chief factors responsible for the observed beneficial effects of local gastric cooling. 1. Inhibition of peptic activity; 2. diminished gastric secretion and 3. decreased blood flow to the gastric wall.

I have been trying to rack my brain to think of other indications for local cooling. It does reduce secretion from the obstructed rabbit's appendix—and were it not that appendectomy is such a simple operation, local cooling of the appendix would most certainly in man, as in the rabbit, suppress secretion and preclude perforation. We have also used the method to advantage in local cooling of the heart with a sac sutured to the pericardium and by perfusing the coronary arteries with cold blood. My associate, Dr. C. W. Lillehei, has since put this experimental technic to good clinical use in open heart surgery.

Were it not that cooling the bowel inhibited its contractile activity, the method could probably be put to good use in extending the reach of conservative intestinal decompression, in the management of bowel obstruction. Certainly aspects of the bowel problem need to be re-examined with special reference to the effects of cold. Cooling will undoubtedly reduce secretion in obstructed intestinal loops. Absorption too probably will be reduced, in consequence of which the distention problem still remains to be dealt with. Mild systemic hypothermia might well prove to be an agency of real worth in the management of intractable diarrhea. It deserves clinical trial, I think.

As Dr. Penick indicated, in the current surgical literature one gets the impression that the entire surgical profession has swung over to the Billroth II procedure and truncal vagotomy. Certainly the papers of the Smithwick group

in Boston, of Edwards and Herrington in Nashville, and Orr and Johnston in London, give that impression. If the good results which they report continue, the proponents of any other operation will have a heavy burden on their hands to come forward with anything as good.

One more thing and I am done: The late Hans Haberer of Cologne, Germany, was a keen advocate of the Billroth I operation. In 1939, he finally had to admit that he had found it necessary to abandon the Billroth I operation for duodenal ulcer, because of the large number of recurrences.

The Billroth I operation should be a physiologic operation, but it fails to cure duodenal ulcer. The reasons are not apparent. When, however, the antrum is removed—and segmental resection affords good evidence that the antrum does protect—removal of the antrum then brings the acid peptic gastric juice of the fundus directly into contact with the duodenum. There remains an area of about 7 cm. to the biliary papilla. An area, moreover, in which no continually operating mechanism exists by which this area can regularly provide itself with adequate neutralizing juices to overcome the peptic digestive quality of the fundic gastric juice. If one measures the pH at the new gastric outlet over a long period of time, he will observe that the pH at the neo-stoma is lowest following the Billroth I operation. That is the reason, I think, why Haberer, almost 20 years ago after having performed more than 2,000 Billroth I operations, was forced to admit the failure of the operation. Whether the Billroth I operation combined with a truncal vagotomy will overcome this handicap of the Billroth I, remains to be seen.

I want to compliment the speakers once again for a very judicious treatment of an intricate and difficult subject.

Dr. I. Snapper:—I must say in all frankness that I have given up the roentgenologic differentiation between benign and malignant lesions of the stomach. After having heard Dr. Cohn's interesting conclusions, I will, in the future, state "Since the lesion is situated in the upper part of the stomach, I hardly think it is malignant."

I am still afraid, however, of ulcerating lesions which are actually situated in the cardia. Most of these lesions are malignant.

I was very much interested to hear that Dr. Wangensteen has again taken up lavage of the stomach with ice water for the treatment of upper gastrointestinal hemorrhage as was popular in Germany 60 years ago but has been considered harmful for many decades.

Dr. Wangensteen:—We have to believe it now.

Dr. Snapper:—Concerning the development of nontropical sprue after gastrectomy as mentioned in Dr. Hardy's paper, the British have performed a small bowel biopsy before a total or subtotal resection of the stomach. The result of

these biopsies seems to indicate that only the patients who already before operation show changes in the villi of the small intestine, will develop sprue after the operation.

Perhaps attention should be given again to the blind loop syndrome of the jejunum which may remain after subtotal resection of the stomach. Occasionally, one sees a patient who, after a subtotal gastrectomy, suffers from a serious form of macrocytic anemia. This can sometimes be cured by the administration of neomycin which sterilizes the blind jejunum loop. Occasionally a resection of the blind loop will be necessary to cure the macrocytic anemia.

Dr. Hardy has seen one or two cases of gastrojejunocolic fistula after subtotal gastrectomy. This, of course, was a very frequent complication after the old-fashioned gastroenterostomy. A Billroth II resection, however, usually eradicates the HCl production and thereby less frequently leads to a jejunal ulcer which can penetrate into the colon.

In a patient with severe diarrhea and cachexia after subtotal resection the possibility of gastroileac fistula must be considered. Even in the cases where the radiologic diagnosis of such a fistula cannot be made a re-operation is necessary.

Dr. Penick has said that 90 per cent of peptic ulcers are cured after operation. This is an excellent result, because medical treatment is only satisfactory in patients who are in a position to put their ulcer in the center of their existence and have enough means to live for their ulcer. If, however, the patient has to earn his living, cannot eat exactly as he chooses, has to go to mediocre restaurants, and cannot leave an inclement climate in the autumn or winter, then the probability of frequent recurrences and complications of the ulcer is very great.

INFECTIOUS HEPATITIS*

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Introduction

This paper represents personal observations and impressions of the author while serving as Chief of the Medical Service of a General Hospital in the Mediterranean Theater of Operations over a period of two years, beginning September, 1943. The first six months were spent in Tunisia, the remainder of time in Italy, four months supporting the Cassino front, 15 miles north of Naples, and the last point of operation being in Leghorn.

From the day of debarkation, hepatitis was the most important problem that confronted the medical service. There was no single month during the entire period of operation that this disease did not head the list from the standpoint of medical admissions (venereal diseases excluded). Hepatitis accounted for more hospitalization days and more evacuations to the Zone of Interior than any other single medical condition.

Strangely enough, hepatitis was observed in our own personnel before our hospital was open for operation. This point is emphasized because through studies of our personnel some knowledge was gained about the incubation period before it was definitely known that this disease was caused by a virus and probably transmitted by the oral intestinal route. Hepatitis without jaundice was first diagnosed in several members of our unit before there was even semblance of proof that such a condition existed and long before the term was introduced into Army medical nomenclature. It was not without considerable resistance that this diagnosis was first ventured, for certainly no one had seen such a syndrome before, and the similarity of this condition to the psychosomatic problems that were always present even left some doubt in the mind of the diagnostician. Now that this condition has a definite place in medicine, those who were loathe to accept it as a clinical entity undoubtedly feel that they had done a great injustice to the soldiers whom they labelled "psychoneurotics".

Since the start of World War II, the literature has gradually been filled with all phases of infectious hepatitis. Experimentally the cause has been found although the virus not isolated. Numerous papers dealing with the epidemiology, pathogenesis, immunity, pathology and clinical picture of hepatitis have been published. The main purpose of this paper is to present personal observations

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of the condition, as seen in 2,250 cases that were admitted to the medical service or as medical consultations in surgical patients. The majority of the views expressed, naturally, are similar to those accepted by the profession and already in print. Some of the observations were original and were forwarded through channels to the Surgeon General's Office in the form of monthly reports. Some of the ideas were shared by other medical men in the same Theater of Operations, and a compilation of the opinions has led to a better understanding of the condition as it exists today.

Frequent references will be made on observations in our personnel, for it was in this group that close observation of all phases of the clinical picture was possible, and much was learned concerning typical manifestations. The attack rate was exceedingly high compared to similar units of equal strength and operating under identical conditions. During two years overseas service, 9 of 100 nurses, 11 of 60 officers, and 65 of 500 enlisted men developed the condition. Seven were evacuated to the United States because of severity of initial attacks, chronicity of mild symptoms or recurrence of condition. One enlisted man died of acute hepatic necrosis during a relapse.

Epidemiology

In keeping with accepted findings of other hospitals in the Mediterranean Theater of Operations, the highest incidence of the disease was during the fall and spring. Being mindful that seasoned troops were less susceptible than newcomers in endemic countries, it was our definite impression that the disease became much more severe in 1944 and 1945 than it was in the fall and winter of 1943, even though we were more alert to the early recognition of the disease; hospitalization was prolonged, and facilities for treatment, especially dietary care was far superior than in our early period of overseas duty.

The fact that newcomers in endemic zones are highly susceptible was clearly brought out by the high incidence of disease in our own personnel soon after arrival in Africa. Within two months after arrival in Africa, 60 members of our unit were hospitalized with jaundice. There are a number of factors to be considered in this respect, among which are: localities of hyperendemicity, sanitary conditions and modes of transmission.

Four other general hospitals arrived in Bizerte, Tunisia, at approximately the same time. Two of the hospitals arrived the same day, one being quartered in an open field, one mile from our own bivouac area; the other, in permanent buildings ten miles away. Two units, which arrived one month earlier, were located six and eight miles away. The incidence of hepatitis in these units was one-tenth that of ours.

It was decided on the day of arrival that the contingent which was quartered adjacent to us would not function as a hospital in Africa but merely stage

there in preparation for transhipment to Italy, which was 80 days later. This camp site was then constructed with screened kitchens and mess halls which took only several days. As our unit was to operate a hospital in this location, construction was immediately started, and due to shortage of material it was thought best by higher headquarters not to duplicate the construction of screened facilities because our stay in temporary quarters would be for only one month. All preparation and cooking of food as well as eating was done in unscreened tents and in the open. It was the concensus that at no time in our lives had we encountered so many flies. At times it was impossible to eat because the flies accumulated in such great numbers. Over 75 per cent of our personnel developed diarrhea within ten days overseas. After great insistence, we were finally allowed salvaged mosquito netting to protect our mess tents. At best it was inadequate, but it did decrease the number of flies which were anxious to share our meals.

Flies are mentioned as a possible source of transmission of the infectious agent. There is no doubt in my mind that flies were the chief source of transmission by contaminating food during our early period overseas. The hospital unit which stayed adjacent to us, having screened kitchens and mess halls, had only five of their personnel go down with hepatitis. The source of water supply and degree of chlorination being the same as for our unit.

An evacuation hospital which was in operation directly across the road from our area with approximately one-half the personnel had no trouble with hepatitis. This unit had nine months more overseas service, and was considered well seasoned. Their water supply and living conditions were identical to ours with the exception that mess facilities were protected. A number of native huts and hovels were adjacent to our area, and even though filth and squalor reigned supreme, none of the occupants were jaundiced during our stay in this vicinity. The latter statement will be brought out in greater detail in factors dealing with immunity.

While the above data speaks strongly for insect transmission, it is felt that transmission by infected water supply was probably the more important factor in the majority of cases. An excellent supportive example was seen just before the war was over in Italy. One regiment of the 10th Mountain Division was pulled out of combat for rest. Their rest area was in a valley of the North Appenines. Companies A and C of 1st battalion were quartered next to each other, with Company B a short distance away. Living conditions were the same for all companies in the battalion. Companies A and C used a common well for the source of their water supply which was adequately chlorinated according to army standards (4 parts to 1 million). Within four weeks approximately 75 per cent of these two companies were hospitalized with hepatitis. This was one of the highest attack rates to hit a segregated unit. There was only one soldier of Company B who was infected. It was subsequently learned that this soldier was

a messenger who daily visited the areas of Companies A and C and drank water which came from the contaminated well.

Later studies showed that chlorination of water as prescribed by army regulations does not kill the virus of hepatitis. While the above example is not irrefutable evidence of water transmission, it is very convincing. Interesting also is the fact that the contaminated well was also the source of water supply for about ten Italian civilian families who still maintained their homes in this area. None of the civilians were clinically ill at this time. They volunteered the information that the same type of outbreak of jaundice occurred in one of the German divisions when they were quartered in the identical area before they had retreated northward.

Evidence of immunity to the virus of hepatitis was certainly obvious in the civilian population of Africa and Italy. The above examples of relative freedom from attacks in the civilians who lived adjacent to our area in Africa and the Italians who lived in the midst of the high infection of the 10th Mountain Division demonstrated that some protection must exist. It was learned that most infants and children in both places have "jaundice" or "liver trouble with fever" while quite young. While the true number of cases of chronic hepatitis or portal cirrhosis in adults is not definitely known, most Italian civilians complain of "liver trouble", and expect sooner or later to become ill with it. This accounts for the popularity of the springs and spas in Italy where the Italians go for their yearly "cure" of the condition. It is believed that a course of mud baths and drinking the mineral spring water yearly will preclude invalidism from liver trouble. This information was obtained from several civilian doctors and a few "intelligent" citizens who had a dread of the disease. It was indeed a mystery for a time why the civilians of Africa and Italy, who virtually lived off the filth and garbage of infected American and British Troops, did not develop the disease. The problem of cross immunity was just a little different. Questioning all patients with jaundice about previous attacks of the disease, it was soon learned that quite a few had been previously ill with jaundice in the United States or in Ireland (2nd Armored Division). Their initial attacks were during the period when hepatitis was rampant in continental United States, and definitely proven to be from inoculation with yellow fever vaccine. Thus there appear to be several strains of the same virus or perhaps a different virus which can cause hepatitis and still not confer immunity for subsequent infection. An interesting example of this was noted in some of the French Colonial troops. Before the final assault on Cassino in May, 1944, several divisions and unattached regiments of French Colonial troops were placed in the line. After 24 hours of combat, 693 French Colonials were admitted to our hospital in one day. Of this number, there were 40 medical patients, the remainder being casualties. Of the medical admissions, approximately 50 per cent had the same complaints and findings, i.e. high fever, lymphadenopathy, pain and tenderness in upper right quadrant and epigastrium, vomiting and diarrhea. Leukopenia

was consistently observed. None of these patients developed jaundice, although a high percentage displayed hepatomegaly. The diagnosis of "hepatitis without jaundice" was ventured—, and as other hospitals who received the same type of patients had a similar experience, it was felt that this was the most probable and likely diagnosis. As their clinical course was rather short, and these patients were not hospitalized too long, eventual outcome as far as complications and sequela was not known. These colonial troops who undoubtedly had some immunity to their own native African strain of the virus were susceptible hosts to an endemic Italian strain. It is very possible that the virus which causes one type of the nonicteric variety of hepatitis may be immunologically different. Refuting this point is the fact that in human volunteers infected with the same strain, some come down with nonicteric hepatitis while the majority do develop jaundice. The answer may be that it is the host's reaction whether he shall be jaundiced or not.

The clue to the probable duration of incubation period in naturally occurring hepatitis was obtained by the rapidity with which this condition developed in our unit. Three weeks following the day of debarkation, our first patient was sent to a station hospital with symptoms suggestive of acute gastrointestinal infection. Three days later this soldier was jaundiced. Within one week 15 members of our unit were hospitalized with the same condition. The remaining number of the original 60 were hospitalized within two months of debarkation.

As the cause of hepatitis was still unknown, various guesses were made. It was even thought that atabrine was the possible agent, for when suppressive therapy was started aboard ship, well over 50 per cent of all passengers had nausea, vomiting and diarrhea. As a new outbreak of diarrhea started soon after we arrived in Africa, it was again blamed. After this cause was definitely ruled out, we were sure that the infectious agent, whatever it may have been, had an incubation period of at least three weeks and probably four in most instances.

Many ideas have been advanced concerning predisposing factors which lowered the soldier's resistance to the infectious agent. These factors are: poor diet, unsanitary living conditions, fatigue, exposure during active combat and alcohol. While all may play some role in isolated cases, poor sanitation and improper sterilization of food and water are undoubtedly the most important factors if troops are quartered in an endemic area.

It was learned that if combat and noncombatant troops occupied the same areas at different times, the attack rate in both was the same even though the service troops were better fed, had less physical strain and had better quarters. This point was brought out by the antecedent history of our first staging area in Africa. After jaundice had taken a nice toll of our personnel, it was learned that this same area was occupied during the last days of combat in Africa by one contingent of an American division and later by British troops. Both had a

very high rate of jaundice when they were quartered here and shortly after moving out, whereas the rest of the troops did not show an unusual incidence of the condition. It was a serious but innocent mistake by someone to bivouac our unit in the already designated "jaundice bowl".

While alcohol is undoubtedly bad for patients convalescing from hepatitis, or for those patients who have mild active disease, its danger as a predisposing factor in lowering an individual's resistance to infection is questioned. There is a definite possibility that if enough alcohol is taken when the agent is ingested through food or water, infection may not occur. Proof of this statement is not forthcoming, but in our officer group which was infected, 8 of the 11 consumed less alcohol than any similar number of our officer corps. The heaviest and moderate drinkers were spared. This could have been coincidence, but for a small group it is noteworthy.

Pathogenesis

While the accepted belief is that the natural occurring form of hepatitis attacks the gastrointestinal tract first, it is entirely probable that the nasopharynx and associated lymphoid tissue may be the site of primary involvement. Supporting the former view is the predominant number of cases wherein the presenting symptomatology is that of nausea, vomiting and/or diarrhea. To a lesser extent, but with definite frequency are those cases wherein the prodromata and initial symptomatology were basically those of upper respiratory or "grippal" nature. At varying times during our overseas services it was not uncommon to see the majority of cases being hospitalized with the above picture. This was especially true for cases which were admitted at approximately the same time and coming from the same locality, or men serving in the same companies or batallions. Later, both groups had the same clinical course; but it is my definite impression that the latter group usually had the higher incidence of the abortive type of disease or hepatitis without jaundice.

Undoubtedly the virus is essentially hepato-tropic and a definite diagnosis of this condition should not be made unless hepatic involvement is present. Other organs and systems are involved as evidenced by those patients who revealed marked lymphoid hyperplasia of nasopharynx, lymphatic adenopathy, especially of posterior cervical nodes, splenomegaly, renal complications and central nervous system manifestations.

The coincident involvement of lymph nodes, spleen and bone marrow, as evidenced by the type of lymphocytic response suggests that the reticuloendothelial system has a definite affinity for the virus.

Persistent evidence of renal pathology in a number of cases, which was definitely thought not to be due to an irritative factor of bile pigments, leads one to believe that the virus may strike this organ.

Clinical Picture

The disease as seen in our hospital should be divided into the following groups:

1. Classical hepatitis with jaundice, acute and chronic.
2. Hepatitis without jaundice, acute and chronic.
3. Atypical hepatitis.
4. Fulminating hepatitis.

The majority of patients, who were jaundiced, gave a history of a preicteric stage which varied from 2 to 10 days; average about 5 days, which usually was as follows: Fever which may or may not have followed chilly sensations. Pain or discomfort in the epigastrium and the upper right quadrant, anorexia, nausea with or without vomiting. Diarrhea usually persisted throughout the preicteric state; malaise, lassitude, headache which at times was severe, more pronounced in frontal and retrobulbar region; arthralgia and myalgia, at times, very severe. Frequently the fever persisted through the preicteric period as did other symptoms, to subside with the appearance of jaundice. At times the above symptoms lasted for only a few days, the patient remaining on duty until icterus appeared, sometime, even noted by a buddy before being aware of it himself. Dark urine was noticed quite frequently, which seemed to be an alarming symptom.

The prevalence of diarrhea in this theater of operation was so pronounced that most soldiers who took ill with the above symptoms were usually treated on duty status with empirical use of one of the sulfa compounds. If symptoms persisted or increased in severity they were then hospitalized. Frequently, acute symptomatology passed off with only residual pain in the upper abdomen or the upper right quadrant and slight intolerance to food. Naturally, this could have been a sequel to the supposed bacillary diarrhea and as most soldiers were conscientious, they remained at their posts until icterus was present. Frequently, the presence of minor abdominal complaints were disregarded; shame and a sense of pride prevented quite a few soldiers from reporting to sick call. It is believed that many thousands of soldiers in this theater had hepatitis either in a mild or abortive form without ever being hospitalized. It is entirely possible that a fair number of patients who were admitted with jaundice and who gave no immediate previous preicteric symptoms were in reality induced relapses, their infection having taken place weeks or months previously. This is especially true for the majority of cases who were diagnosed as hepatitis without jaundice.

To a lesser extent, especially in certain groups of admissions, the preicteric symptomatology was characteristically that of an upper respiratory or grippal infection; gastrointestinal symptomatology being present just before jaundice appeared. The presenting picture in quite a few preicteric, nonicteric or abor-

tive cases resembled that of primary atypical pneumonia, sandfly fever, or suppressed malaria so closely that differential diagnosis was extremely difficult.

In a large group of patients who were not hospitalized early in the preicteric state or in those who remained on duty with hepatitis without jaundice, the following symptoms were common: Sensation of fullness in upper right quadrant with dull pain over the liver which usually became more severe with activity during the day. Exertion, riding in vehicles over rough terrain usually intensified the discomfort. The sensation of fullness in the abdomen was noticeable while in bed and marked difficulty was encountered trying to get into a comfortable position. Lying on the right side caused pain and a sensation of crowding in the abdomen. Lying on the left side gave a sensation of dragging and pulling. Lying flat on the back usually caused a marked pulling of the lower abdominal muscles. The most comfortable position was on the back with the knees slightly flexed. The above discomfort undoubtedly accounted for the high incidence of insomnia. Lassitude and intolerance to exercise was always prominent. Vertigo, dyspnea and palpitations aggravated by the slightest exertion were common complaints.

The above complaints were also common in those patients who were convalescing from an acute attack of hepatitis or in those who had the disease in a mild chronic form. Combat, separation from families and loved ones, basic inadequacies all tend to bring out the psychosomatic trends in an individual. There is no doubt that this factor played an important role in the aggravation and exaggeration of symptoms, and unless each case was individualized and careful observation maintained, even the experienced clinician could be fooled. To me, the mistake was made more often in the opposite direction; that is, many soldiers were labeled psychoneurotics with anxiety and conversion states, when in reality they were suffering from the disease in a chronic form with some functional coloring. It was not uncommon to go on the neuropsychiatric service and find patients with variegated complaints who had physical findings and even laboratory confirmation of disturbed liver function.

With the appearance of jaundice in acute hepatitis, subsidence of symptoms was the rule. Temperature returned to normal, appetite improved with no nausea or vomiting. Abdominal pain, usually minimal, was present generally after meals, especially if the amount of food consumed was excessive. In a fair number of cases postprandial distress was present until the icterus had reached its peak. Diarrhea or frequent bowel movements persisted longer than any single symptom. In a few cases low grade fever persisted throughout the course of jaundice and coincided with the degrees of bilirubinuria. Itching and bradycardia were never prominent except in those patients who were jaundiced for a considerable period. Tachycardia was noted more often in those cases who had persistence of symptomatology and evidence of active disease.

In a fair number of cases, arthralgia and myalgia continued in a marked degree in the early icteric period. At times, this was so severe, analgesics were necessary.

The duration as well as intensity of jaundice was variable; shortest period being 4 days and the longest, 4 months plus. As it was necessary to evacuate patients with chronic illness, at least 10 patients were sent back to the United States with jaundice of more than 3 months' duration. The highest icterus index was 288 units and the highest serum bilirubin was 36.5 mg. per cent; the average length of icteric period being 20 days, and the average maximum icterus index about 50 units. As a general rule, patients were kept in bed for 30 days providing icterus and symptoms had subsided within this period. If jaundice was present for only a week or 10 days this period was shortened.

With the disappearance of jaundice and return of sensation of well being patients were allowed graduated exercise during the period of convalescence with return to normal diet. If symptoms recurred the patient was put back to bed and laboratory studies were repeated to evaluate the intolerance to exercise and physical findings were carefully observed. During the period of convalescence approximately 8 per cent relapsed with jaundice. About 5 per cent of the patients had a relapse of jaundice before they were allowed out of bed, these soldiers usually had persistence of abdominal discomfort, anorexia, intolerance to food and infrequently, low grade fever after clearance of the first attack of jaundice. The term "induced relapse" was designated for the first variety whereas "spontaneous relapse" was relegated to the latter type. In a much smaller number induced relapses appeared after the soldiers had returned to duty. Although the criteria for discharge to duty were supposedly uniform throughout the theater, it was found that some hospitals deviated from the standard policy and discharged their patients before convalescence was entirely complete or disregarded subjective complaints volunteered by the patients. The greatest number of relapses were found in this group. The importance of the relapse can be realized by the serious outcome that may ensue. Of the five deaths which presumably were caused by the naturally occurring type of disease, three died in a relapsing form. The exodus in all three was rapid, occurring in 3, 6 and 7 days after reappearance of jaundice. One patient was returned to duty with a low grade fever and minor gastrointestinal symptoms. A check of the record from a former hospital revealed that no laboratory studies were done previous to discharge. Another patient relapsed one month following recovery from an apparently benign course of disease with no untoward symptoms during the convalescent period. The third patient, a member of our group, relapsed after being discharged from the hospital two months previously with what appeared to be a stormy case of hepatitis without jaundice. He had been on duty, was closely watched, had no definite symptoms until he celebrated at a New Year's party, taking several drinks of liquor with his friends. Nausea and vomiting occurred the following day, jaundice appeared the next, and death

occurred four days later. Whether alcohol was contributory to his relapse is not definitely known; several other relapses had been seen following overindulgence, fortunately the outcome was different. A definite impression was made on a number of cases in our unit who had recovered from hepatitis; on their own accord they gave up alcohol unhesitatingly.

Relapses without jaundice were noted more often than with icterus. The question always arose whether these were cases of the chronic active variety which had not completely recovered, or whether a true relapse was present. The picture simulated that of the preicteric stage, more often it took the form of the insidious variety of nonicteric hepatitis with intolerance to exercise, marked fatigability, anorexia, weight loss and gastrointestinal symptoms of varying degree. The liver was usually enlarged and tender; although in some, no definite enlargement could be noted.

The persistence of symptomatology with or without liver enlargement sums up the picture of chronic infectious hepatitis. Only those who have had it can fully appreciate the discomfort and disability it causes. The residual dyspepsia for greasy and fried foods is a constant reminder that choice of diet is important for a sense of well being. Heaviness and a dragging sensation in the upper right quadrant which usually follows undue exertion is pronounced at times. Fleeting, sharp pains in the same location with radiation to the lumbar region may be very severe. Abdominal distention and flatulence may be persistent or evanescent. Bouts of diarrhea alternating with constipation in an individual who previously had normal bowel habits are indeed disconcerting. Cyclic periods of fatigability with headache and mental depression are common. Tasks which were once easily accomplished, at times appeared insurmountable. Short bouts of unexplained fever may appear from time to time.

The similarity of the syndrome to anxiety or conversion state is marked and quite frequently the patient is undecided whether his symptoms are real. He only knows that he feels bad and is anxious for some relief. Tension, anxiety, and preoccupation with body functions play a major role in the precipitation or aggravation of symptoms; but even in periods when no motivating factor is involved symptoms will occur.

In the fulminating cases, anorexia and vomiting were the most outstanding symptoms. Jaundice increased rapidly. Mental confusion, disorientation and stupor were constant and ominous findings. Oliguria which was progressive was noted in all patients who died. Peripheral edema and ascites occurred if the patient lived long enough after urinary suppression occurred. Spider hemangiomata developed rapidly as did purpuric manifestations of the skin and mucous membranes. Vomiting of blood and passage of blood in stool was observed in all fatal cases. Delirium and coma accompanied by fibrillary twitchings and convulsions were constant findings. Fever which was low grade at start gradually increased with terminal hyperpyrexia. Terminal pulmonary edema and

vasomotor collapse was the usual mode of exitus. Blood pressure showed no remarkable deviation except before exitus when it was in keeping with systemic collapse.

The atypical forms of hepatitis, wherein the clinical picture showed involvement of other organs even after the hepatic disturbance was improved or cleared, were of considerable interest, and often taxed the diagnostic acumen of the clinician.

Hematuria and albuminuria early in the disease, was seen often enough to conclude that some renal involvement was present. Whether this was a larval nephrosis or irritative phenomenon from bile pigments, is difficult to say. Whether this was a definite complication from viral infection is more likely; against the irritative theory, is the fact that with increasing jaundice and progressive biluria, unless severe, urinary findings usually subsided.

In a small number of cases, albuminuria persisted in considerable amounts, and increased in quantity as the condition progressed. This occurred in face of clearing of the hepatic picture. Hematuria, to a less extent, also accompanied the albuminuria. Cylindruria also occurred, but in negligible quantity. There was no elevation of blood pressure and no azotemia. Edema only occurred in those patients who displayed a significant lowering of plasma proteins. No marked impairment of concentrating or diluting power of kidneys was present as observed from the various kidney function tests. Antecedent history in these patients failed to reveal any suggestive history of nephritis. The picture resembled that of a subacute glomerular nephritis; and in a few cases with a complicating nephrotic syndrome.

Because of persistence of urinary findings, and in keeping with the theater policy, 20 such patients were evacuated to the United States for definitive treatment and disposition. Their final outcome is not known.

In a smaller group of patients, the above renal picture was seen without any associated or previous history of hepatitis. Etiological diagnosis was difficult to make, with the absence of any confirmatory evidence of viral infection; it was necessary to evacuate these patients with the accepted diagnosis of "active subacute glomerular nephritis". It became known to us that a similar picture was seen in German troops. One German hospital, which was inspected soon after V-I day had 30 such patients on a medical ward at one time. Their attending doctors were also fascinated by the occurrence of such an unusual condition, but as they had seen the picture during their entire stay in Italy, it was labelled "trench nephritis". Poor living conditions, exposure and malnourishment were listed as the causative factors; although the condition existed when all was going well with the Germans in the early part of the Italian occupation and campaign. As many medical men have not had enough experience with this condition, it still remains somewhat obscure. Thorough study will probably

yield more information and it is possible that a new medical entity will be added to our ever increasing number of virus diseases.

Physical Examination

In the preicteric state, findings which resemble those of other acute viral infections were often noted. Reddened hypertrophic changes of the lymphoid tissue of oropharynx with cervical adenopathy was quite common. Posterior cervical adenopathy usually persisted through the icteric period and well into convalescence. Its presence in chronic hepatitis was an important finding, changes in size with associated tenderness usually coincided with periods of exacerbation of systemic symptoms.

Cervical adenopathy occurred in 70 per cent of all admissions. Some epidemics revealed this finding in a minority of patients, whereas at other times all patients admitted displayed this finding. Enlargement of glands elsewhere was observed only on rare occasions.

Splenomegaly occurred in 17 per cent of admissions. The incidence of enlargement was noted much more often in certain periods when the admissions were from certain localities, or with seasonal variation.

Splenomegaly occurred almost invariably with the jaundiced variety whereas cervical adenopathy was noted in both icteric and nonicteric groups.

Hepatic enlargement is the most constant finding in hepatitis. It occurred in over 95 per cent of cases. The degree of enlargement varied from an organ which was just barely palpable to one which extended below the umbilicus and even to the iliac crest.

Tenderness to palpation varied with individual cases and did not coincide with the extent of the enlargement. It was noted more often in the early cases and at times perceived in the upper right quadrant before definite enlargement of the organ occurred.

The duration of hepatomegaly also varied, from early in the preicteric state to subsidence of jaundice as the general rule. Some patients were left with a mild degree of enlargement even after complete disappearance of symptoms.

Enlargement was the rule in chronic cases, with or without jaundice. Progressive enlargement usually heralded relapses or exacerbation of disease.

The size of the liver was noted to vary considerably during a period of hours. It was not uncommon to check a patient on morning ward rounds with no enlargement whereas in the afternoon, increased size could be felt with ease. Exercise would often enlarge an organ which was otherwise not palpable, this was especially true in the chronic cases who had symptoms invoked by physical exertion.

With livers which were slightly enlarged, manipulation by palpation would often displace the organ so that it could not be felt. This was indeed a curious finding and was first noted when cases were checked with the ward officer in charge and our findings would differ. The actual demonstration of this finding spared embarrassment of the junior officer.

In patients who were severely jaundiced, *spider angiomata* and pin point hemorrhages of the skin and oral mucous membrane were noted.

Morbidity and Mortality

The average duration of hospitalization from date of onset of illness to date of return to full duty was 51 days. Eighty-seven per cent of all cases fell into this category. In our earlier period of operation, duration of hospitalization averaged 35 days. It was definitely thought that the disease ran a much milder course. Later on, when the number of relapses increased and the disease appeared to be more severe; more rigid criteria for discharge, of necessity, lengthened the period of hospitalization.

Approximately 6 per cent of cases were reclassified to a limited duty status because of presence of mild symptoms or evidence of some hepatic dysfunction as learned from liver function test (bromsulfalein excretion).

The remainder of patients, with the exception of 6 fatal cases, were evacuated to the United States because of severity of initial attacks with persistence of jaundice; chronic hepatitis with residual symptomatology and laboratory confirmation of disturbed fever function; more than one relapse; extrahepatic complications, usually renal involvement.

Infectious hepatitis caused more hospitalization days in our installation than any other single medical condition. The highest census at one time being 570 patients in October, 1944.

Pathology

The findings at postmortem were similar in all six cases with only minor difference. This was in one case which presumably died of homologous serum jaundice. His duration of illness from the time of appearance of jaundice was five weeks. On section this liver revealed an increase in fibrous tissue in the periportal and perilobular spaces with evidence of cellular regeneration, the remainder of liver tissue revealed evidence of subacute yellow atrophy.

In the five remaining cases; the duration of terminal illness being very short; the livers showed evidence of a mixture of red and yellow atrophy. There was slight enlargement of all organs, the outstanding feature on gross examination being the hemorrhagic appearance and loss of normal consistency.

Fixed sections revealed diffuse necrosis of parenchymal cells in all stages of degeneration. In some areas, vacuolization with cloudy swelling was present. Infiltration of polymorphnuclears and lymphocytes in the interlobular and periportal spaces was a striking feature. Bile thrombi were noted in the smaller canaliculi and hyperplasia of lumen was seen in some areas.

The three livers which came from the relapsing cases showed more fibrous tissue replacement and more inflammatory cell infiltration than the two which came from patients dying in an acute fulminating primary attack.

Kidneys revealed mild swelling; cut sections revealed tubular degeneration in various stages with presence of bile thrombi and bile casts. Tubular epithelium showed evidence of bile pigment in the degenerating cells.

Enlargement of mesenteric nodes with cellular hyperplasia was distinctive in the fulminating cases.

Hemorrhage throughout the gastrointestinal tract was a constant finding. Petechial hemorrhages in the brain and brain stem were noted in all cases.

Laboratory Examinations

The erythrocyte count was usually found to be of normal value. In a few cases of chronic hepatitis mild secondary anemia was noted. In patients who were severely jaundiced over a considerable period, the same finding was observed. No case of macrocytic anemia was observed in our series of patients.

The white count varied from normal to a slight leukopenia or mild leucocytosis. As a rule, during the febrile period, leukopenia with relative lymphocytosis was the common finding. In a small number of cases the lymphocytosis was not unlike that seen in infectious mononucleosis, the number of young cells with cellular changes not being as marked. Eosinophilia was never encountered with any regularity to make this finding noteworthy.

The erythrocyte sedimentation rate was used routinely as one of the aids in evaluating activity of the disease. This test has not been found of much value in hepatitis by most workers. To us, the test agreed more often with clinical evaluation of the patient than any single laboratory aid. During the acute stage of hepatitis, mild to moderate elevation was consistently noted. With clinical improvement and return to normal of liver size, coincident fall in sedimentation rate was the general rule. In patients, who complained of residual symptoms and when definite hepatomegaly existed, elevated rates were present. Increased rates were consistently present in those patients who maintained a persistent low grade fever. With rare exceptions, increased rates were found in those patients who exhibited abnormal bromsulfophthalein retention.

There was no great alteration in the plasma proteins unless the patient was severely jaundiced over a long period of time, or in a few patients who exhib-

ited peripheral edema. All fatal cases, however, showed a definite reduction in blood proteins, invariably reflected in the albumin fraction.

Blood sugars showed no variation from normal in the usual acute or chronic case. In patients with severe jaundice moderate hypoglycemia was noted. In all fatal cases definite hypoglycemia was observed. As these patients were judiciously treated with glucose infusions most of the time it was difficult to obtain blood samples without the obvious increased value for the administered glucose. When this influencing factor was obviated, levels of 60 to 80 mg. per cent were not uncommon. In one patient, blood sample was taken just before death with a value of 40 mg. per cent being obtained. This patient had more convulsive seizures than the other fatal cases.

Decreased prothrombin levels was the usual finding in those patients who exhibited bleeding tendency. In a few patients who show only cutaneous purpuric manifestations, no pathological abnormality was found.

Blood chemistry for nitrogen retention revealed normal findings in the majority of cases. In severe hepatitis with jaundice mild elevations of NPN paralleled the high icteric index. In all fatal cases, azotemia, which was rather marked, occurred with cholemia. An interesting and consistent finding which was of great prognostic value although of ominous significance was the progressive lowering of the blood urea nitrogen in the face of an increasing nonprotein nitrogen. All fatal cases displayed this finding. When divergence of these values was noted and progression in this direction continued, a fatal outcome could always be predicted.

Our findings in urinalyses were always more revealing than in other hospitals in our theater. Thinking that there may be some error in reports from the laboratory due to inexperience of the technical help, these findings were checked by the senior pathologist and results confirmed.

Albuminuria, ranging from a trace to two plus was the usual finding in initial specimens in the early icteric period. This was present in 70 per cent of all admissions. The albuminuria was usually transitory and passed off in most cases before the peak of jaundice had set in. In those cases where definite renal complication was present, albuminuria was constant for long periods and continued until the time that these patients were evacuated to the United States.

Microscopic hematuria was also a feature which was reported by our hospital more consistently than from other insitutions. Twenty per cent of all admissions revealed this finding in significant amount to make it a characteristic finding in the early icteric case. Hematuria like the proteinuria was a transitory finding and passed off concurrently with it. Bilirubinuria and urobilinogenuria was always observed in keeping with the expected findings of hepatocellular and obstructive jaundice. Urobilinogenuria in significant amounts was observed in the preicteric state to give a clue to the diagnosis. The dilution method with

Ehrlich's aldehyde, being the simplest method, was the test of choice. Reactions of 1/80 or higher were regarded as significantly positive. Positive tests were also obtained consistently in the presence of clinical malaria, but were never progressively increased as in hepatitis.

With the presence of acholic stools or marked biluria, urobilinogen was absent, to return in very high dilutions once the jaundice started to clear. The gradual diminution in urobilinogen was then a sign of improvement and usually coincided with recovery. In patients who displayed low grade activity in the posticteric state, positive tests were usually present. More often, in hepatitis without jaundice, even with considerable hepatic enlargement and in the presence of definite symptomatology, the test failed to reveal positive results. While this test was considered one of the most sensitive and reliable to pick up liver dysfunction, its failure was not regarded as absolute proof that liver disease was not present. It is entirely possible that after a time of impaired function, hepatic cells can eliminate adequate amounts without any retention being present.

The necessity to have a procedure which was simple and could be repeated often to study progress of the many cases in the hospital at one time automatically led to the use of the icterus index as the test to measure the amount of pigment in the blood. As it did not require specialized technical skill, the results were considered accurate and consistent. Serum bilirubins were done less often and most of the time in borderline icteric indices or in hepatitis without jaundice. It was found, that in those cases where a deciding determination was most important, the results were often on the borderline and a definite statement could not be made whether an abnormal amount of bilirubin was present in the blood. The test was also very time-consuming, and in overworked laboratory personnel, accuracy of quantitative estimations was always questioned.

The ideal test for qualitative or quantitative dysfunction in nonicteric hepatitis was found wanting. The laboratory evaluation of a pathological state, when the question of mild dysfunction is present, is not always final. It was impossible to run all the liver function tests on every questionable case, for experience had taught us that results did not always correlate with the clinical picture, and if a mistake was to be made it would be safer to err with clinical judgment.

Once it was known that hepatitis was a serious problem as far as sequela and relapses were concerned, attention was focussed on laboratory evaluation. It was necessary to obtain certain laboratory procedures before clearance could be given for discharge of a patient. Certain tests in this direction were advocated by higher headquarters.

The first two tests recommended for liver function were the hippuric acid excretion test and the alkaline serum phosphatase reaction. Both proved to be of little value and were time-consuming to the laboratory. The results seemed

more often to be out of line with the clinical picture than supportive or confirmatory evidence in either a positive or negative sense. It was found that if these two tests would be used as criteria for discharge of a patient to duty, many of the sick ones would have been the first to go whereas a number of those who were clinically cured would in all probability be hospitalized to this day waiting for laboratory clearance. After insistence of many of the hospitals concerning the futility of these tests, a directive was forwarded rescinding the use of these procedures.

Much attention was focussed on the cephalin cholesterol flocculation test. This test was also found of limited value in our experience. In the presence of epidemic hepatitis with jaundice its importance as a diagnostic aid cannot be rated high. All jaundiced cases with few exceptions revealed a 3 or 4 plus reactions. The nonicteric cases gave varying results from 0 to 2 plus. The preicteric cases displayed positive reactions with varying strengths. The posticteric cases also gave varying results and were not consistent enough in correlation with the bromsulfalein test and clinical picture to warrant its use as a deciding factor. It was not uncommon to find a patient with a 3 plus reaction showing no retention, whereas one having a 0 to 1 plus reaction showed 40 per cent retention in one-half hour. While the test is not advocated as one for the estimation of liver function but as an index of active injury to parenchymal cells it appears that the results should have been more uniform.

The occasion did not arise when this test was necessary to differentiate obstructive from nonobstructive jaundice. It appears, that some members of the profession are using this test as the deciding factor in the differential diagnosis. From observation in a few jaundiced patients with hepatitis who developed a positive reaction only after being icteric for a period of time, a warning is sounded that a serious mistake may be made if too much reliance is placed on this laboratory procedure.

Of all the liver function tests which were used for the evaluation of hepatic dysfunction, the bromsulfalein test was the one found to be most satisfactory. In the diagnosis of hepatitis without jaundice its assistance was extremely valuable. In evaluating latent symptomatology in a convalescing or chronic case, the results were gratifying. While this test in a negative manner did not rule out the presence of disease, the results were consistent enough to depend on.

The standard dose of 5 mg. per kilo of body weight was used with samples drawn at 30 and 60 minutes. While normally no dye should be retained at the end of an hour, it was arbitrarily decided that retention of 10 per cent or more in 30 minutes and 5 per cent or more in 60 minutes constituted evidence of enough liver dysfunction to warrant further observation.

It was not uncommon to find a patient who had 20 to 30 per cent retention at the end of an hour without any symptomatology. Careful observation usually

revealed that such a patient, if allowed full activity, would either relapse or have manifest symptomatology after a period of time.

This test was advocated by some as a diagnostic procedure in the preicteric state. Its use for this purpose can only be decried, for if a patient will develop jaundice, one will not have to wait too long for its appearance. In a few cases who were given the dye in a forward echelon for diagnosis and then sent to our institution for hospitalization, it was found that they had the disease in a much severer form, both from standpoint of intensity of jaundice and severity and duration of symptoms.

The procedure is not an entirely innocuous one, in addition to the possibility of causing a relapse especially if repeated in too short an interval, it has other complications. Of 1,250 examinations, 6 patients developed a thrombophlebitis at the site of injection of the dye. It is entirely possible that this occurred more often, but in a minor form so that the patient did not report it. One patient developed bilateral pulmonary infarction from an antecubital thrombosis, the second pulmonary infarct occurring after the axillary vein was ligated and the thrombus removed. Fortunately complete recovery ensued. Three patients were thrown into acute asthmatic seizures following the administration of the dye. There was no immediate antecedent history of asthma in these individuals, although one gave an allergic history as a child.

Summary

Impressions as to etiology, epidemiology, pathogenesis and immunity in naturally occurring viral hepatitis are reviewed as gained from personal experience with 2,250 cases.

The clinical picture of this disease is reviewed in all manifestations as noted in the Mediterranean Theater of Operations in World War II. Variations of the clinical picture are emphasized with attention focussed on the atypical, relapsing and fulminating cases.

Discussion

Dr. I. Snapper:—Dr. Blitz' paper illustrates the excellent work which has been done by several of our military medical units working under unfavorable circumstances. As a matter of fact, the concept that epidemic jaundice is actually due to a hepatitis is a discovery which was made during the *first* World War. Until that time the term "catarrhal jaundice" was used to designate this disease.

Virchow, probably nearly a hundred years ago, at an autopsy of a patient with hepatitis found a mucus plug in the common duct. This plug in his opinion was the cause of the jaundice. He therefore coined the term catarrhal jaundice,

i.e. jaundice due to a superficial inflammation of a mucus membrane—in this case of the common duct.

Before the first World War autopsies of patients with catarrhal jaundice were practically nonexistent and Virchow's concept was generally accepted. Epidemic jaundice raged during the First World War as it did during the Second. Hospitals which admitted patients with jaundice were bombed. At the autopsies of the casualties the mucus plug of Virchow was not found. Since then the degeneration of the liver cells as the cause of epidemic jaundice was emphasized and the name hepatitis introduced.

It is remarkable that now—40 years later—it has become doubtful whether the concept of hepatitis is *completely* correct. In long-standing cholangiolitic jaundice drainage of the common duct usually results in rapid improvement of the jaundice.

This might well indicate that an inflammation of the common duct, compromising the free flow of bile, could at least be a contributing factor in the causation of the jaundice in hepatitis.

I was happy to hear that Dr. Blitz insists upon the danger of exertion for a hepatitis patient. I have seen so often in the Orient that when patients get up too early and start their routine work, relapses occur which are worse than the original attack of hepatitis.

I have an open mind as to whether the virus of the hepatitis is or is not transferred by insects. The transfer of typhoid by flies is certainly not accepted anymore.

Dr. Oscar Blitz:—I think it is important to stress once again, even though a patient is jaundiced for only several days, it does not mean he is clinically well when icterus disappears and harm can come by placing patients on full exercise programs when this finding alone has abated.

I believe the present policy of the armed forces is to keep the jaundiced patient at complete bed rest until icterus reaches its maximum. If there are no symptoms, they are allowed up. I think that this may be rushing matters and the possibility of inducing relapses or prolonging the course of illness is more probable than with a more conservative attitude. Chronicity of symptoms, physical findings and abnormal laboratory results are seen more often in the patient that is pushed too quickly in the early stages of illness.

SUPRA- AND TRANSDUODENAL EXPLORATION OF THE COMMON BILE DUCT*

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Good judgment often necessitates the employment of surgery as a therapeutic measure howsoever reluctantly at times this may be accepted; and the surgeons' technical problems are bound to be reflected in the results of the clinicians. What is done and how it is done at the operating table may result in complete restoration of health or continued disability. Great progress has been made in preoperative and postoperative care of patients. Likewise, advances have been made in the technical features of surgery. More experience with biliary tract operations has resulted in improvements in technic and this has brought about diminished risk and more definitive and complete cures.

The present report mainly concerns methods of obviating benign obstructive lesions of the common bile duct and as a basis for study cites an analysis of

TABLE I

Cholecystostomy only		6
Cholecystectomy only		315
Cholecystectomy and choledochostomy		90
Choledochostomy only		34
Gallbladder left in	13)	
Gallbladder previously removed	20)	
Congenital absence of gallbladder	1)	

445 operations for benign lesions of the biliary tract on a private surgical service. In this group the common bile duct was explored 124 times. Included in the series are concurrent cases of pancreatitis because of the frequent association of pancreatitis and biliary tract obstruction and the controversial part ampulla obstructions play in the etiology of pancreatitis.

The operations in the group are shown in Table I.
A further analysis of this group of cases is shown in Table II.

Combined supra- and transduodenal operation to remove stones from the common bile duct is not new, for the transduodenal approach was employed successfully by McBurney[6] in 1898, but surgeons have had the greatest reluc-

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tance to open the duodenum and have employed it only when a stone was impacted in the lower end of the common bile duct which could not be removed otherwise. This attitude was the result of a fear of duodenal fistula and an unfounded thought that it would most surely occur if the duodenum was opened and closed. Therefore, the duodenum was rarely opened to obtain information

TABLE II

GALLBLADDER AND COMMON DUCT OPERATIONS

	Deaths	
Total operations	6 (1.3%)	445
Common duct explorations		124
Combined supra- and transduodenal (Stones found 24)	1	58
Supraduodenal only (Stones found 18)	2	66
Sphincters cut		49
Stenosis (Group in which duodenum was opened)		40
Jaundice		54
With stones (Stenosis 7)		29
Without stones (Stenosis 13)		25
Stenosis (7 had stones)		20
Pancreatitis		11
Stones		42
With jaundice (Stenosis 7)		29
Without jaundice (Stenosis 4)		13
Stenosis		11
Pancreatitis		25
Jaundiced		12
Common ducts explored (Stones 5)		24
Duodenum opened		13
Ampulla cut		12
Divulsed		1
Gallbladder removed		15
Gallbladder previously removed		4
Gallbladder not removed		6

about the condition of the distal end of the common duct until very recent years. A paper presented in 1948[7] on combined supra- and transduodenal exploration of the common duct met with silent rejection from most quarters. Since then, however, this technical approach has been widely accepted. Wangensteen has gone so far as to say that within the last three years, when operating for stones in the gallbladder, he has adopted the precept of opening the duodenum to

inspect the ampulla of Vater because of the frequency of stenosis when stones are present. The standardization of proper indications for the use of this method remains a problem for surgeons and this will be affected both by the increased ratio of total cures and the risk of employing the combined approach.

The advantages of opening the duodenum when exploring the common bile duct are several. In removing stones from the common duct the surgeon then is working at the end and the middle of a tube, not just through an opening in the middle. By opening the duodenum soft tissue obstructions may be visualized; pancreatitis and stenosis of the ampulla, a real organic obstruction, may be obviated by ampullotomy, and carcinoma of the papilla of Vater may be discovered and proper operation (pancreatoduodenectomy) be undertaken. This lesion, easily overlooked otherwise, was found twice during the period this series of 445 benign lesions was being operated upon. One of these patients was cured by pancreatoduodenectomy. The condition in the other having been overlooked three times elsewhere during common duct exploration recurred after local removal. Three times in our series of duct explorations, stones were known to be left in. These all occurred when the approach used was only the supraduodenal one. A higher percentage of stones were removed when the combined supra- and transduodenal approach was employed (50 per cent) than when the supraduodenal only was employed (27 per cent). This is partially influenced by our attitude that if stones are found in the common bile duct it is an advantage to open the duodenum.

Surgeons would be most accurate if they would open the common duct every time there is obstruction, either from stones or from soft tissue such as pancreatitis or ampullitis or from carcinoma at the end of the duct, but never open it when there is no obstruction. Using present prevailing indications for opening the common duct, the ratio of found obstruction to exploration does not indicate such accurate results. Not opening the duct when obstruction is present becomes a tragedy for the patient necessitating a subsequent exposure to the risk of another operation. Therefore, a certain percentage of negative explorations is acceptable. In the various series reported in the literature for operations on the biliary tract exploration of the common duct is done from 11 per cent[5] to 45.7 per cent[3] of the cases. This is a wide variation. In our experience exploration of the common bile duct is performed in approximately 28 per cent of the operations for benign lesions of the biliary tract, but stones were recovered in only 30 per cent of those in which the common duct was opened; the obstruction in the remainder if present being attributable to the soft tissue changes (pancreatitis, ampulla stenosis or periductal edema). In the group in which obstructive jaundice was present (54) stones were recovered in (29) 54 per cent. Soft tissue obstruction was the cause of jaundice in the remainder and the three major explanations for this are: 1. periductal pressure from edema of the gastrohepatic omentum associated with acute or subacute cholecystitis; less commonly 2. stenosis of the ampulla of Vater and 3. pancreatitis. Stones were

found in the common duct in 9.4 per cent of the entire group of cases. This percentage for stones in the common bile duct is close to that reported in other series in the literature, even when the duct was explored in a higher per cent of cases (45.7 per cent) as reported by Colcock. Glenn and Johnson reported an incidence of recovery of stones in only 7 per cent when the common duct was explored in only 11 per cent of operations for benign lesions of the biliary tract.

The surgeon is justified in opening the common duct in patients with jaundice or the history of it even though some explorations will be negative for stones, for if he does not heed this indication for duct exploration he will leave common duct stones in some patients and he will fail to find and obviate some soft tissue obstructions of a permanent nature. Furthermore, other indications for duct exploration such as ectasia or induration of the duct or pancreatitis may at times yield negative results. This is justified in order not to leave obstructions and stones by making the indication for duct exploration too rigid.

It is interesting that when stones were recovered from the common bile duct in this series, jaundice was present in approximately 54 per cent of the cases and it was absent in 46 per cent. This clearly demonstrates again that absence of jaundice does not preclude the presence of stones in the common bile duct.

Pancreatitis

Pancreatitis was found at operation in 5.6 per cent of our cases. In all cases of benign lesions of the common bile duct when pancreatitis is included as suspected before or only discovered at operation its incidence will be approximately one in 18 cases. This will coincide with clinical evidence of the severity of some of the attacks, and with radiation of the pain through to the back which justifies the suspicion of associated pancreatitis.

In many instances it is possible to accurately make the diagnosis of pancreatitis before operation, particularly when it is severe such as acute hemorrhagic pancreatitis. But it is difficult to say that chonic pancreatitis or recurrent pancreatitis is or is not present preoperatively unless laboratory evidence, not always positive becomes incontrovertibly so, such as recurrent high amylase or lipase or the presence of calcareous deposits in the pancreas or the excessively widened duodenal loop detectible by roentgenographic examination. Under these circumstances the clinical diagnosis can be apprehended with more or less certainty but there is another group of cases, by far the larger group, in which no positive clinical evidence is found, only a suspicion that pancreatitis might be present and in this group pancreatitis can nonetheless assuredly be diagnosed at the operating table.

It is important for the surgeon who is operating upon a benign lesion of the biliary tract to explore the abdomen most carefully to ascertain the condition of

the spleen, the esophageal hiatus opening, the stomach, the liver, the kidneys, the duodenum, the gallbladder, the common duct and the pancreas, and unless there is some contraindication to do it ascertain the condition of the structures in the lower abdomen. If one has a routine about such a maneuver in the earlier part of an operation, conditions, which subsequently may lead to postcholecystectomy syndrome, will not be overlooked. Furthermore, it is only by a careful routine of this sort, that mild pancreatitis may be picked up in the absence of acute hemorrhagic variety with the intense edema, the huge mass and the evidence of fat necrosis. Even in the absence of fat necrosis, sometimes the pancreas is twice as large and twice as hard as it normally is and this undoubtedly is pancreatitis. The increased consistency in size of the gland justifies the diagnosis of chronic or recurrent pancreatitis even in the absence of evidence of a more acute form. In this series we have carefully checked the pancreas at operation; 5.6 per cent of patients who have operations for benign lesions of the biliary tract have evidence of pancreatitis.

In the group of cases reported here, evidence at operation was found to justify the diagnosis of pancreatitis in 25. Usually the findings were enlarged hard pancreatitis; three times, however, fat necrosis and massive edema was present and in one of these hemorrhagic fluid. In 24 cases the common duct was explored; in one the process was too violent and decompression was obtained by cholecystostomy. None of these cases died. All of them recovered. Minor recurrences are known to have occurred in one patient and reoperation and transduodenal ampullotomy at a second procedure was necessary in one.

Stenosis of the Ampulla of Vater and Ampullitis

Physiologists, pathologists and surgeons have accepted the idea that among other causes for stones in the biliary tract probably the major factor is stasis. The idea that all stones found in the common bile duct are there only after traversing the cystic duct is also widely accepted. After all if obstruction is a factor practically all of it could be at the termination of the common bile duct, and this would affect not only the common bile duct but would also affect the gallbladder. What percentage of stones found in the common bile duct were formed in that structure is not clearly known; perhaps it is very high. There are other factors in the formation of gallstones. They will not be discussed. But it is important to realize that obstruction at the end of the common duct can and does at times cause stones to form primarily in the common duct. The best proof of this is the fact that in 27 per cent of the reported cases of congenital absence of the gallbladder[4] stones were found in the common bile duct.

Comparison of Supraduodenal and Combined Supra- and Transduodenal Exploration

In our group of cases although approximately half of the common duct explorations were performed by the combined supra- and transduodenal method

and another half by the supraduodenal method only, the mortality has not been greater in the group in which the combined method was used. As a matter of fact, only one of these patients died in the hospital.

There were two deaths in the group in which the supraduodenal approach only was used. This does not indicate, of course, that the combined supra- and transduodenal approach to the common duct is a safer method; it is not. It means that when it is done with care and with precision, it may be done with an acceptable mortality, and in our hands the risk has not been increased. On the other hand, we have had reports of increased risks and we would warn that it must be used judiciously and with technical precision. In order to use it correctly, the duodenum has to be mobilized, cutting the peritoneal reflexion on the right, then displacing the duodenum and head of the pancreas anteriorly. A transverse incision in the duodenum is better than a longitudinal because it has to be closed on the greater circle and if an incision is made longitudinally and closed transversely, it is more apt to cause tension. A very small incision is all that is necessary, and with the sound in the common duct through a supraduodenal opening, the end of the sound may be impinged against the duodenal wall and it shows very definitely where this opening should be made. If it is indicated, the ampulla is cut and usually when the duodenum is opened there is indication for doing an ampullotomy. Very careful closure of the duodenal incision should be made using a continuous chromic catgut suture with an inverting secondary layer of interrupted fine silk stitches. Transnasogastric suction should be employed a little longer in the postoperative care of these patients. Oral feedings are withheld for 72-96 hours.

In estimating obstructions of the common bile duct at the time of exploration it is not always clearly evident when a probe commonly known as Bakês dilators has traversed the ampulla of Vater. The ampulla of Vater is very mobile and it may be pressed against the opposite wall of the duodenum giving the impression that the sound has traversed the ampulla when in reality it has not and on opening the duodenum one finds that the ampulla itself is being displaced. It is reasonable to assume that a 2 mm. dilator would pass readily through the ampulla of Vater. When it fails to do so, spasm of the sphincter has been given as the cause for the interference, but in my experience it is not this. The sound passes through the sphincter all right but there is a tight little stenotic meatus similar in every respect to that seen in the submaxillary salivary duct when a stone is present there, and this has to be forced by abruption or cut in order to get the sound through the duct. This stenosis of the ampulla of Vater is not imaginary; it is an organic defect and it can be the cause of stones in the biliary tract or the cause of pancreatitis. In such cases the meatus and sphincter should be cut. These cases have been reported by a number of authors[2,7,8,9] and it is now well substantiated and widely accepted that this clinical low-grade obstruction does occur. Probaly it is one of the frequent causes of pancreatitis.

Our indications for exploring the common bile duct by the supraduodenal method are as follows: 1. An enlarged dilated duct; 2. the presence of jaundice or the history of previous jaundice; and 3. evidence of pancreatitis, 4. a palpable stone in the duct.

We do not open the common bile duct simply because there are multiple small stones in the gallbladder. This would raise the number of common duct explorations exceedingly high, approaching the higher percentage given by some able surgeons, but we feel that under these circumstances the percentages of negative explorations will be too high.

Our indications for opening the duodenum after making a supraduodenal opening in the common bile duct are as follows: 1. The presence of multiple stones in the common bile duct when there is any doubt about their complete removal or the passage of the sound freely into the duodenum; 2. the presence of pancreatitis; and 3. the uncertainty as to whether the sound has passed into the duodenum.

The contraindications to opening the duodenum are as important as the indications and frequently the contraindications come into play. They should be rigidly observed because if they are not, the risk of the combined procedure is increased. Contraindications to the use of the combined approach even though the indications are present for it, should prevent its use. The contraindications are: 1. Massive edema of the gastrohepatic omentum and the duodenum such as is frequently found with acute cholecystitis; 2. the presence of acute hemorrhagic pancreatitis; 3. in debilitated patients; and 4. in very old patients unless there is a strong indication necessitating it such as a stone known to be impacted in the ampulla of Vater.

Operations for acute cholecystitis deserve special comment. These operations in the presence of intense edema and induration can be one of the most difficult technical procedures a surgeon is called upon to do. Justifiably, under these conditions, particularly in series operated upon by inexperienced surgeons at the residency level such as those reported by Becker[1] and by Glenn[5] resort to cholecystostomy alone is understandable and laudable. This saves lives by avoiding technical errors such as injury to the common bile duct in areas of induration where it cannot clearly be identified. In spite of statements to the contrary elsewhere, injuries to the common bile duct made in this section of the country which subsequently came under our care were made while the inexpert surgeon was operating for acute cholecystitis. This is understandable and is to be expected. They had more difficulty seeing where they were and tragically proceeded blindly. Better a cholecystostomy and a second operation than this. In the acute case with intense edema sometimes it is not safe to insist on more, since identification of the common duct can be most difficult even after removing the edematous gallbladder from fundus down to the cystic duct. We do not like to and rarely use cholecystostomy since it is only an interval operation

leaving another to come; but we do not hesitate to employ it when we think otherwise we might lose the patient. Furthermore, even when justifiable indications exist for exploring the common bile duct, contraindications may countermand such action, particularly under certain instances of acute infection when clear identification of the common duct is not feasible without accepting exceptional hazard.

Summary

A series of 445 operations for benign lesions of the biliary tract was analyzed and used as a basis of study. Some of the difficulties in judgment concerning technical features of common duct operations are discussed. The advantages of doing a combined supra- and transduodenal exploration of the common bile duct were enumerated and the indications for opening the duodenum, which were employed in this series in approximately 50 per cent of the explorations of the common bile duct, were given. They include multiple stones in the common duct when there is any doubt of their complete removal, the presence of pancreatitis, and doubt as to whether the sound has passed transvaterianally into the duodenum. The combined approach can be a technical help in removing stones from the common bile duct and in obviating soft tissue obstructions. Contraindications to opening the duodenum are enumerated. They are frequently present and they should be rigidly observed. The comparative safety of the combined method when it is indicated and not contraindicated is shown by no increase in mortality when this method was employed. It is admitted, however, that it does have features which normally would increase risk and, therefore, it should not be employed without clear indications and without the most meticulous and careful technical application.

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Discussion

Dr. O. H. Wangensteen:—The presentation of Dr. Mahorner is a harbinger, I believe, of what surgeons will presently be doing, if they have not already adopted technics such as he described.

In our clinic over a period of many years, I have been doing something very much like what Dr. Mahorner has been telling us. I recall that Dr. Snapper sent me a patient a number of years ago, who had previously been operated upon for gallstones and who continued to have residual pain. I noted that Dr. Snapper while watching the procedure grew a bit apprehensive as I opened the duodenum and prepared to do a sphincterotomy. Dr. Snapper assures me, however, that this more aggressive surgical attack upon the problem of an atretic terminal common bile duct resolved the patient's problem of persistent biliary dyskinesia.

Dr. Cattell of the Lahey Clinic has described fibrosis and narrowing of the biliary papilla as a result of gallstones. Most writings on the subject are in general accord with Cattell's attitude, I would infer. A number of years ago, I began to look at the problem in an exploratory manner, having also had experiences such as Dr. Mahorner outlined for us today. Over a period of five years, we have been pursuing the problem more diligently. Whenever gallstones are encountered in the gallbladder, we explore the common bile duct. A No. 3 Bâkes' dilator is passed into the duct, and if with ease, it can be passed through the papilla, the ampulla is considered to be normal. Anatomists who have studied the structure of the common bile duct and the papilla suggest that the normal papilla is 5 to 10 mm. in diameter. In other words, a No. 3 Bâkes' dilator should pass quite readily. If the slightest suggestion of resistance is encountered in passing this dilator, force should not be employed. The surgeon, if right-handed, would be well advised to go to the left side of the table, then holding the duodenum in his left hand, he passes the Bâkes' No. 3 dilator with his right hand. If resistance is encountered and the tip of the dilator does not pass readily into the duodenum, the surgeon should make a short transverse duodenotomy. In fact, this is my practice. Two 5-0 silk sutures are anchored at opposite sides of the duodenum, just where the end of the probe came up against the duodenal wall, when it failed to pass the papilla. A short transverse incision is then made. There are definite advantages in the transverse incision. If the surgeon places it correctly, it will lie directly over the papilla. Moreover, the short transverse incision is readily closed without leaving the "dog ears", which always constitute a hazard, when the surgeon attempts to make a transverse closure of a longitudinal incision in the bowel. In fact, when an enterotomy is made in the bowel, I do it in this manner. With the papilla in sight, the surgeon tries once again to have the No. 3 Bâkes' dilator pass through the duct into the duodenum. Many times, the papilla is pin-point affording obvious evidences of an atretic ampulla. A 5 per cent solution of Cyclaine is painted on the papilla. I also inject some

into the common bile duct through a catheter inserted through the choledocotomy opening. One waits a few minutes, and then tries again. On a few occasions, following this maneuver, I have observed a papilla which would not permit the passage of a probe dilator and permit not only a Bâkes' No. 3 and a No. 4, but also a No. 5 or even larger dilator without difficulty.

The more usual situation, however, is that, following the application and installation of the Cyclaine, the situation remains the same: the probe cannot be passed.

It is my practice then to cut off the tip of the ampulla. My associates, Drs. Theodor B. Grage and Kamil Imamoglu have studied these histologically. Occasionally, they report finding evidences of an inflammatory lesion. The fibrosis which Dr. Cattell has described, Dr. Grage informs me is a rare finding, at least in our experience. In a discussion on cardiospasm [*Ann. Surg.* **134**:3 (Sept.), 1951] I suggested that perhaps biliary dyskinesia might be an achalasia of the terminal common bile duct, owing to an absence of the parasympathetic ganglion cells. Unfortunately, however, as far as I have been able to learn since, studies of the ganglion cells in this area have yet to be made. It obviously is a study which needs to be done. One not infrequently sees thickening of the sphincter a few mm. proximal to the tip of the papilla, not when he performs sphincterotomy for an atretic ampulla. Moreover, determination of variations in thickness of this muscle is probably also in order.

My colleagues and I have not been able to resolve the nature of the narrowing of the papilla which we have encountered so frequently in gallstones. Our own observations would indicate that when gallstones are found, a narrow papilla is present in approximately 60 per cent of instances. My colleague, Dr. Kamil Imamoglu, has pursued this same study in patients coming to autopsy. He finds that an atretic ampulla in the absence of gallstones is a very rare occurrence. When gallstones are present, findings not unlike those encountered in surgical patients with gallstones are observed. In other words, approximately 60 per cent of patients, who are found to have gallstones at autopsy, will have a very narrow or atretic ampulla.

When we became aware of the consistency of these findings at operation, I persuaded my colleagues, Drs. John F. Perry, Jr., and Kamil Imamoglu, to pursue this inquiry in the laboratory. They applied cellophane tape, impregnated with dicetyl phosphate to the terminal common bile duct, tying loosely over a German silver probe, one mm. in diameter. Employing this technic, they were able to produce gallstones in virtually the 100 per cent of trials in the rabbit and with a lesser frequency of gallstones in dogs and monkeys [*Surgery* **42**:623 (Oct.), 1957]. It is important that obstruction of the common bile duct be *incomplete*. If the obstruction becomes complete, gallstones are not produced.

It is to be recalled that Aschoff and Bacmeister (1909) wrote a monograph on gallstone production and emphasized the element of infection, excepting

only the cholesterin stone. Aschoff toured this country in 1924 and delivered a number of lectures. He then stressed more than in 1909 metabolic aspects and factors in the genesis of some gallstones.

If one excises the gallbladder of the rabbit and then obstructs the common bile duct, as I have just described, gallstones will form in the common duct in 100 per cent of instances. If one applies a ligature to the common bile duct and similarly obstructs the cystic duct, stones opaque to x-rays will develop in the gallbladder.

Drs. Allen Boyden and Maud Gerdes (*Surg., Gynec. & Obst.* **66**:145, 1938) in making cholecystograms of the gallbladder during pregnancy, observed considerable slowing of the emptying time. Within a period of a few weeks following termination of the pregnancy, when x-ray pictures were repeated, emptying of the gallbladder was normal again, in most instances. More recently, we have set about to try to ascertain whether the common bile duct is dilated in the terminal months of pregnancy, much in the manner in which one observes dilatation of the ureter, after the first trimester of pregnancy. Today, roentgenologists are far more sensitive over the taking of x-ray films during pregnancy. We found it necessary therefore to wait until the baby had been born. Directly thereafter, biligrafin was given with the cooperation of our obstetricians. No dilated common bile ducts have been observed. In other words, the delay in emptying of the gallbladder during pregnancy is not owing to obstruction to outflow of bile by the enlarged uterus.

At this juncture, my son, Steve, at present a surgical intern at Columbia Medical Center, who then was working in our experimental laboratories, suggested the possibility that the hormones of pregnancy might be responsible for the delay in emptying the gallbladder. We then set ourselves to the task to determine whether or not gallstones could be produced by the administration of hormones. We began with the rabbit and found that by the concomitant administration of progesterone and estrogen over a period of several weeks, gallstones resulted in both male and female rabbits. We are now in the midst of trying to ascertain whether the administration of these hormones will cause delay in emptying of the gallbladder. If they do, it would be reasonable to infer that the greater frequency of gallstones in pregnancy is owing to the delayed emptying of the gallbladder occasioned by the hormones of pregnancy.

What causes the narrowing of the terminal papilla which Dr. Mahorner has so nicely described, remains a good question without a satisfactory answer. Obviously, the matter needs to be pursued further. There is one additional bit of information which you might be interested in. Whereas the common bile duct is lined by a columnar epithelium, it is sensitive to injury by the digestive juices, as is the squamous epithelium of the esophagus. This was a surprise finding. My colleague, F. S. Cross, now of Cleveland, and I (*Proc. Soc. Exper. Biol. & Med.* **77**:862, 1951) observed that when bile and pancreatic juice were perfused

through the esophageal lumen, erosion of its squamous epithelium occurred. It might well be that narrowing of the papilla is owing to the enzymatic activity of pancreatic juice and bile upon the sensitive epithelium of the common bile duct. This question too needs to be pursued further. I hope that Dr. Mahorner will complete his very nice presentation by giving us his own personal ideas concerning the nature of the atretic ampulla.

Dr. I. Snapper:—Dr. Mahorner emphasized the low fatality of the transduodenal exploration of the papilla of Vater during a gallbladder operation. I do not doubt for one moment that this statement is correct as long as he himself performs the operation. I would like to surmise that in the hands of other less experienced surgeons—even in the hands of Dr. Mahorner's residents—the procedure has a much higher fatality.

Dr. Howard Mahorner:—As to my impression of what is happening to the ampulla, we have this rule: If a 2 mm. dilator doesn't pass, the ampulla is cut. The failure to pass has nothing to do with the muscle. It goes through the sphincter to the tiny meatus but it won't go through the stenosed opening. One might regard the cause of the constriction as either congenital or due to a recurrent inflammation and resulting partial obstruction.

I, too, must warn that transduodenal approach to the common bile duct carries more risk. Duodenal fistula is a possible complication. Fortunately, it hasn't been encountered in our series but when the transduodenal approach was employed by men at residency training level on one of the Charity Hospital services several years ago, it had to be stopped because they were getting duodenal fistulas. The operation must be done with technical precision. When it is indicated, it can be done with a risk that is acceptable and with less over all risk for the patient. Suppose you leave stones in the common duct;—if you go back, you are adding to that risk in a secondary operation. It is a disaster for that patient to have to go through another procedure; therefore, one must be careful and get them out at the first operation.

The series of cases reported here are from a private service.

THE SPLENIC APPROACH TO THE PORTAL CIRCULATION*

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The intimate relationship of the splenic and hepatic circulations is well known. The spleen drains directly into the portal vein, and the success of splenoportography attests to this relationship (Fig. 1). Atkinson and Sherlock[1] demonstrated in man, and we[2] in man and dogs, that with a needle in the splenic pulp it is possible to record a reproducible pressure that is a faithful reflection of the portal pressure. Simultaneous readings of the portal and intrasplenic pressures made with saline manometers in anesthetized dogs show close agreement between these values. Figure 2 illustrates graphically how closely the values approximate each other as the portal vein is alternately occluded and released. Further studies in anesthetized dogs revealed the quick response of the intrasplenic pressure to pharmacologic agents that alter the level of portal venous pressure. Figure 3 illustrates graphically the effect of Gynergen®, angiotonin, epinephrine and histamine on the intrasplenic pressure when injected intravenously into the anesthetized dog. It is also possible to follow the intrasplenic pressure in trained unanesthetized dogs with explanted spleens. In such an animal the known effect of pituitrin[3] in lowering portal pressure was again noted, and Figures 4 and 5 show the drop in intrasplenic pressure in dogs both with a normal portal pressure and in 2 animals with experimentally produced portal hypertension after intravenous injection of surgical pituitrin. It will be noted that in both animals with portal hypertension the intrasplenic pressure returned to a normal level for a prolonged period.

In man, many technics for recording portal pressure have been used. Direct approaches include percutaneous portal puncture[4], hepatic venous wedge pressure[5], intraesophageal varix puncture[6], intrahepatic portal branch puncture at the time of liver biopsy, and the intrasplenic technic.

The technic of recoding intrasplenic pressure in the human is simple. With a 26 gauge, 1½ in. needle, a one per cent solution of procaine is infiltrated into the ninth intercostal space on the left in the middle to posterior axillary line.

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After the cutaneous wheal is made, the needle is slowly advanced with repeated aspiration until paradoxical respiratory motion is noted and blood is freely aspirated through the needle. A long, flexible, number 22 spinal needle is substituted and the intrasplenic position is verified again by aspiration of blood. Pressure may be recorded by a simple spinal fluid saline manometer, a phlebomanometer, or an electromanometer.

Complications may occur, the most common of which is postpuncture bleeding, but in approximately 350 punctures performed by us, bleeding occurred in only 3 patients, 2 of whom required transfusion of one pint of blood and in none of whom was splenectomy necessary. Incision followed by drainage for evacuation of an old hematoma was necesary at a later date in one instance.

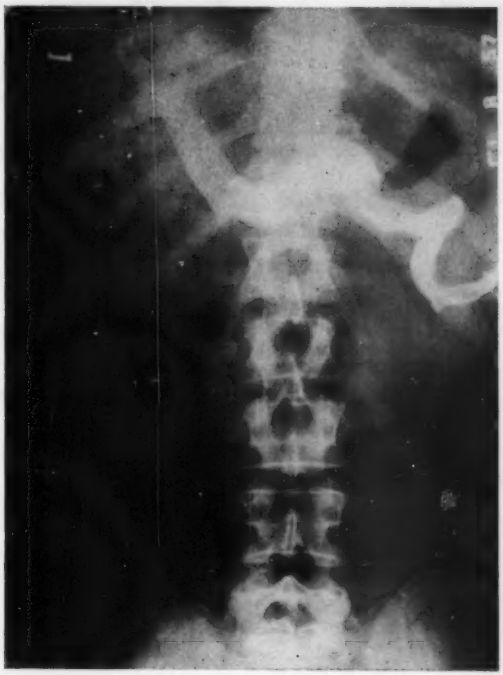

Fig. 1—Splenoportogram of a patient with cirrhosis and portal hypertension. Film made during the last part of injection of dye into the spleen. Direct drainage of splenic vein (right) into portal vein (left) is illustrated.

Comparison of portal pressures estimated by the intrasplenic technics, the hepatic wedge technic, and direct portal puncture during liver biopsy in 21 patients is shown in Table I. Close agreement will be noted for the pressures

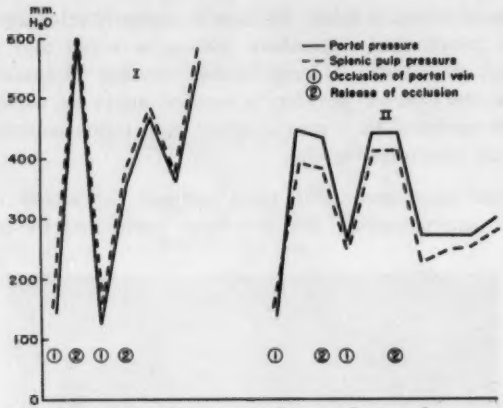

Fig. 2—Simultaneous values of portal venous and intrasplenic pulp pressures in anesthetized dogs.

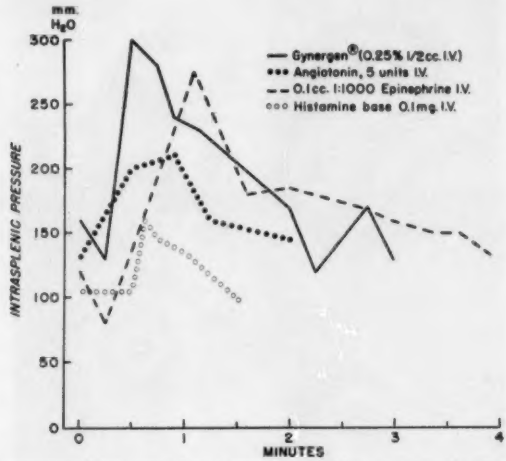

Fig. 3—Effect of various drugs on the intrasplenic pulp pressure in the anesthetized dog.

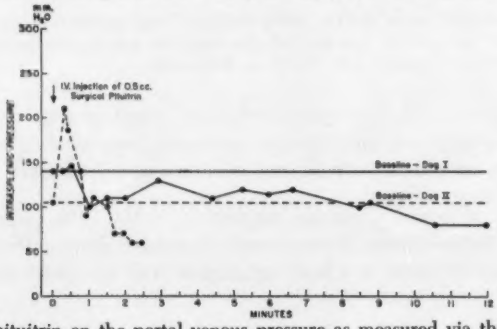

Fig. 4—Effect of pituitrin on the portal venous pressure as measured via the explanted spleen of unanesthetized dogs.

of the different technics. In studies of the intrasplenic pressure in patients with acute infectious hepatitis an increase was noted at the height of the illness usually with return to normal pressure as resolution ensues[7]. Pressures have been determined by this technic in patients with a variety of diseases (Fig. 6). The values in normal patients corrected to 4 cm. retrosternally at the second costochondral junction are 101 ± 29 mm. of saline. In Figure 6 essentially normal pressures are seen for patients with convalescent hepatitis, and mildly

TABLE I

COMPARISON OF PORTAL PRESSURE IN MAN AS MEASURED BY THE INTRASPLENIC PULP, HEPATIC VENOUS WEDGE AND DIRECT PORTAL METHODS*

Case No.	Intrasplenic Pressure	Hepatic Wedge Pressure	Direct Portal Pressure
1	120	140	120
2	430	430	
3	310	295	
4	350		300
5	350	345	
6	230	190	
7	170	140	
8	250	225	
9	140	155	
10	300		320
11	235	250	
12	340	320	
13	180	180	
14	100	100	
15	165	110	
16	85	70	
17	400		300
18	380		285
19	350		320
20	420		365
21	370		390

*(Reproduced from *Gastroenterology*, **34**:52, 1958).

elevated pressures for patients with acute hepatitis. The tendency toward elevation in fatty liver and mild cirrhosis is slight, but elevation in most patients with advanced cirrhosis is pronounced. Elevation was also noted in patients with chronic hepatitis and those with congestive heart failure.

Repeated determinations of the intrasplenic pressure have been of use in following the changes of portal pressure in instances of hepatitis and cirrhosis.

Figure 7 presents the clinical findings and intrasplenic pressures of a patient with moderately severe infectious hepatitis. Correlation of the microscopic changes in serial liver biopsies and the level of portal pressures reflects a moderately high pressure associated with extensive inflammation, continuing eleva-

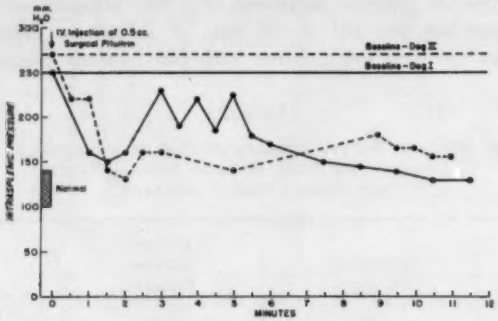

Fig. 5—Effect of pituitrin on the intrasplenic pulp pressure of unanesthetized dogs with portal hypertension and splenic explants.

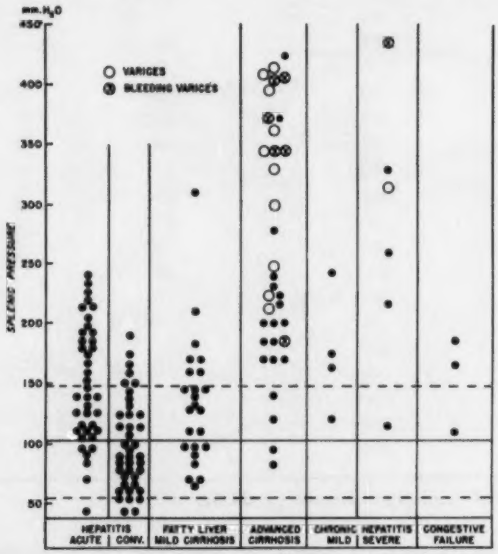

Fig. 6—Scattergram of results of intrasplenic pressure measurements in patients with a variety of diseases. (Reproduced from *Gastroenterology*, **34**:52, 1958).

tion as regeneration occurs, and chronic inflammation is seen in the portal spaces, but return to the baseline as these changes merge into residual focal fibrosis and scarring.

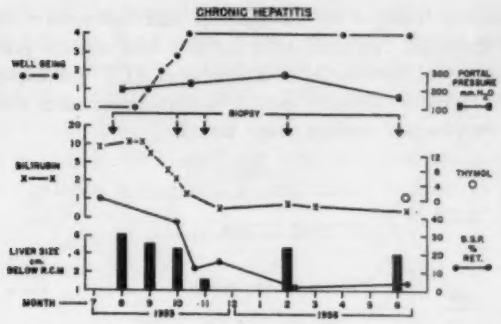

Fig. 7a

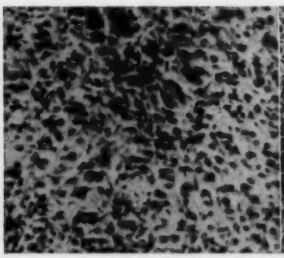

Fig. 7b

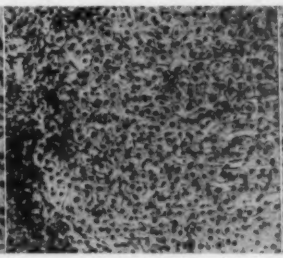

Fig. 7c

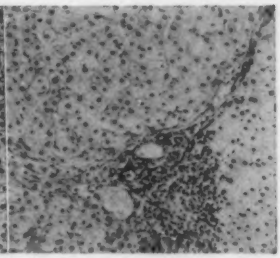

Fig. 7d

Figs. 7a, b, c and d—Chart of clinical course and photomicrographs of consecutive liver biopsies in a man, aged 37 years, with prolonged infectious hepatitis. Note that the portal pressure elevation coincided with subsidence of parenchymal reaction. R. C. M. = right costal margin. (Reproduced from *Gastroenterology*, **34**:52, 1958).

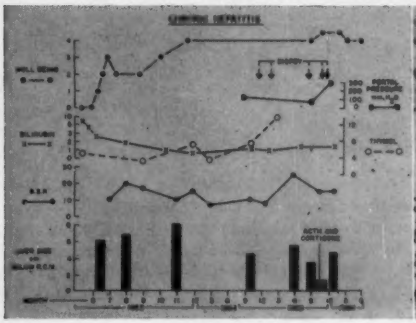

Fig. 8a

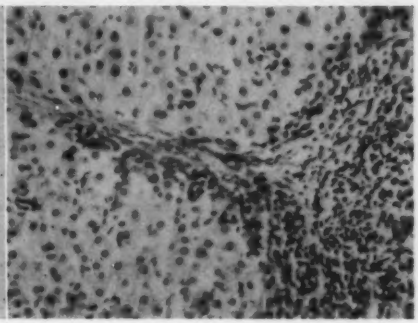

Fig. 8b

Figs. 8a and b—Chart of clinical course and photomicrograph of liver in a man, aged 29 years, with postnecrotic cirrhosis. R. C. M. = right costal margin. (Reproduced from *Gastroenterology*, **34**:52, 1958).

Figure 8 shows changes in the clinical and laboratory observations in a patient with postnecrotic cirrhosis, who initially had normal portal venous pressure and no esophageal varices. After a course of ACTH, however, re-evaluation of the pressure revealed definite portal hypertension, and on esophagoscopy moderate-sized esophageal varices were noted.

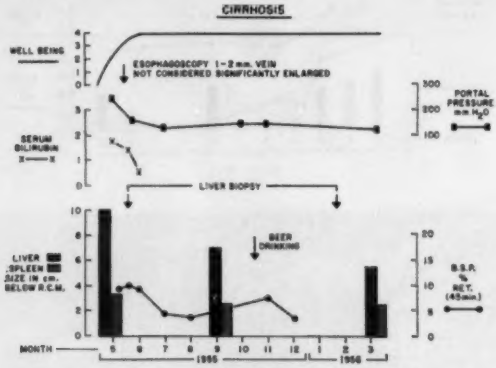

Fig. 9a

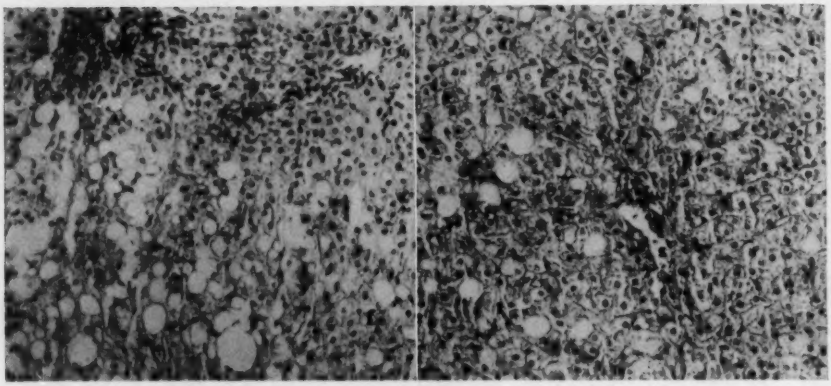

Fig. 9b Fig. 9c

Figs. 9a, b and c—Chart of clinical course and photomicrographs of consecutive liver biopsies in a man, aged 48 years, with mild alcoholic cirrhosis. Note the mild portal hypertension which returned quickly to normal pressures. R. C. M. = right costal margin. (Reproduced from *Gastroenterology*, **34**:52, 1958).

Figure 9 depicts the course of a patient with mild alcoholic cirrhosis and moderate elevation of the portal pressure; as the acute changes in the liver reverted toward normal, the elevated portal venous pressure also returned to a normal value.

A more significant elevation of portal pressure in a moderately severe case of cirrhosis is depicted in Figure 10. Rather extensive portal fibrosis with fatty infiltration and inflammation was demonstrated in the first biopsy. As these changes regressed, the intrasplenic pressure dropped but remained elevated at a rather high figure.

It has been reported elsewhere[7] that pituitrin produces a dramatic fall in portal pressure in patients with portal hypertension. Such an effect is illustrated

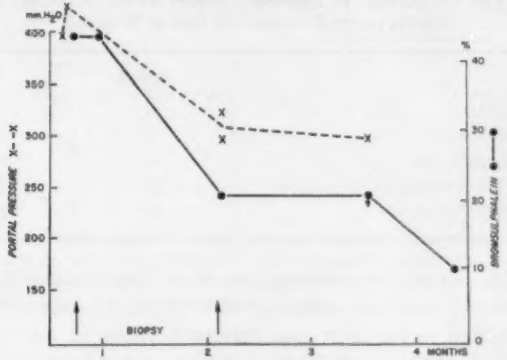

Fig. 10a

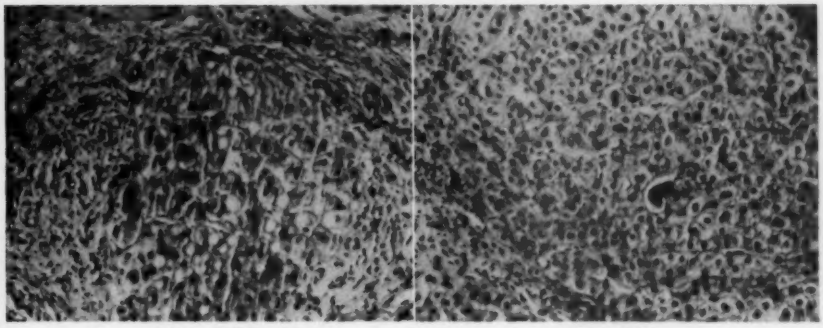

Fig. 10b Fig. 10c

Figs. 10a, b and c—Chart of portal pressure, results of bromsulfalein test and photomicrographs of consecutive liver biopsies in a man, aged 57 years, with severe alcoholic cirrhosis. Portal pressure, which was initially high, decreased with clinical improvement but remained somewhat elevated.

in Figure 11. This drop is accompanied by loss of turgescence of the varices and diminution of hepatic blood flow.

Use of the spleen as a pathway for injection of indicator material in the determination of hepatic blood flow has also been reported[8]. When such an indicator as I^{131} labeled serum albumin is used, an externally placed scintillation

counter permits estimation of the hepatic blood flow without the necessity for catheterization of the hepatic vein. Curves of this type are illustrated in Figure 12. The effect of pituitrin on these curves is shown in Figure 13. This is accompanied by prompt diminution in hepatic blood flow but without change in

TABLE II

CIRCULATION TIMES OF VENOUS PORTION OF THE CIRCULATION MEASURED FROM SPLEEN TO ARRIVAL IN BRACHIAL ARTERY AFTER INTRASPLENIC INJECTION OF RADIOACTIVE SERUM ALBUMIN

	Average	Range
Spleen to liver	2.4	1.5-4
Spleen to liver peak activity	9.5	7-12
Spleen to hepatic vein	13	9-15.5
Spleen to T ½ descent activity in liver	20	15.5-24
Spleen to brachial artery	28	24 -33

cardiac output or hepatic oxygen uptake. It is also evident that intrasplenic injection of iodinated radio-albumin makes it possible to detect the circulation time from the spleen to the liver and various portions of the venous drainage of the liver with the use of catheters, and to peripheral arterial channels with

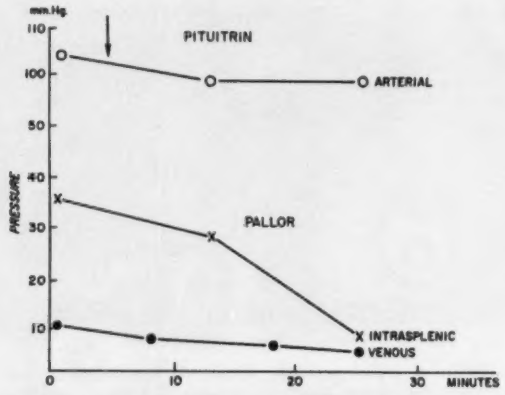

Fig. 11—Effect of pituitrin on intrasplenic arterial and peripheral venous pressure of a 24-year old man with cirrhosis of the liver. (Reproduced from *New England J. Med.*, **256**:108, 1957).

the use of external scintillation counting. Average figures for these determinations in a number of patients are shown in Table II.

The principal application of these technics for measuring portal pressure is not at present in evaluation of the condition of individual patients, although

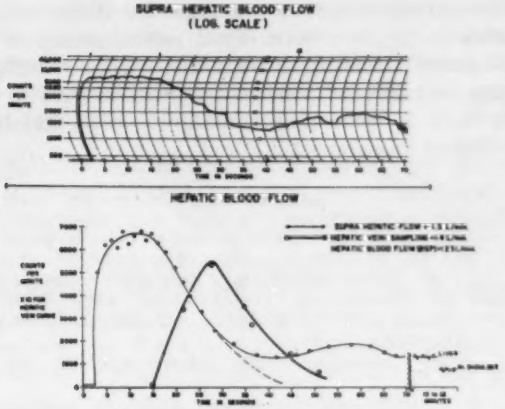

Fig. 12—Curves of dilution of I^{131} labeled serum albumin after intrasplenic injection. Top curve was recorded over the liver externally with scintillation probe and right lower curve was determined from serial samples of hepatic vein blood. Hepatic flows calculated from both curves agreed closely.

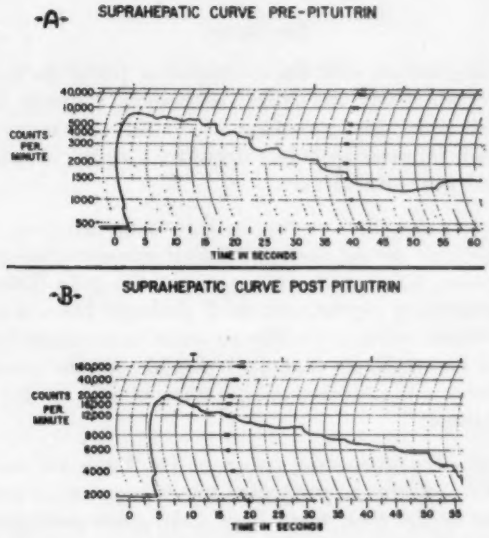

Fig. 13—Effect of intravenous injection of pituitrin on curve of dilution of I^{131} labeled serum albumin in portal venous circulation of the intrasplenic injection. (Reproduced from *New England J. Med.*, **256**:108, 1957).

they may be of great value in certain instances of undiagnosed gastrointestinal bleeding, but rather in the elucidation of the natural history of the pathologic physiology of the portal circulation during various forms and phases of hepatic disease. When this information is available, it may be possible to select those patients who are likely to bleed from esophageal varices and to subject them to prophylactic surgical procedures.

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Discussion

Dr. O. H. Wangensteen:—Dr. Davis' studies of portal pressure by percutaneous puncture of the spleen are indeed interesting. I should like to ask him whether he has observed any peritoneal hematomas accompanying such procedures. Getting this information before definitive surgery, obviously, is an item of great help in orienting the surgeon.

The success of local gastric cooling, which device we have employed with some success in patients having increased portal pressure—this device does not depend upon pressure. It has to do only with two things: 1. Diminished gastric secretion and inhibition of peptic activity; 2. Reduced blood flow. A combination of these two items makes it possible to arrest hemorrhage from esophageal varices as well as peptic ulcer, making it possible for the surgeon in certain patients to go ahead with an elective operation as soon as the patient's vital signs become stabilized.

Dr. I. Snapper:—The interesting curves of Dr. Davis are fascinating. Most of the surgeons who perform the portacaval anastomoses on my patients measure the portal pressure at the time when they make splenoportograms before the operation.

Medicine goes in cycles. When I was young everybody did splenic punctures. When I reached maturity splenic punctures were considered dangerous;

now everybody does splenic punctures again. I agree that the dangers of splenic punctures have been exaggerated. But I want to single out polycythemia as a disease where splenic puncture should be avoided. The spleen in polycythemia is so mushy that at least in this disease serious hemorrhages are liable to occur during splenic puncture.

Sometimes polycythemia is combined with a liver cirrhosis, so-called Mosse's disease. If, in such a case a portacaval anastomosis would be considered necessary, then I would not be in favor of doing a preoperative splenoportogram.

Dr. William D. Davis, Jr.:—Dr. Wangensteen, I did not intend to imply that portal venous pressure elevation is the cause of bleeding esophageal varices. Bleeding is very much dependent on the acid peptic digestion factor, which is an extremely important one. It has been said that portal hypertension has nothing to do with variceal bleeding, however, our statistics are in disagreement with this view.

So far as the puncture is concerned, it has been a relatively safe procedure in our hands. We have done over three hundred punctures with three episodes of bleeding. One required transfusion and did not require splenectomy, and one eventually required evacuation of the hematoma.

NONSPECIFIC MESENTERIC ADENITIS*

AARON LIEBERMAN, M.D., F.A.C.G.

Mexico, D.F.

After a thorough review of the medical literature written on this subject, we have not been able to decide the question as to whether this pathological entity can be considered as a fact, or is it always a consequence of another systemic process whose etiology remains uncertain.

We do know that every year authors find new etiological factors that reclassify some cases considered before as nonspecific mesenteric adenitis; and we also have had the experience of finding cases in our practice, whose only finding was that of enlargement of the lymph nodes in the mesentery, at the time of operation, with no specific pathological relation.

We do not intend here to complete a study of differential diagnosis between nonspecific adenitis and all other diseases that can cause an enlargement of mesenteric lymph nodes, although we will refer to some of them in the following paper.

Historical Data

It seems that Wilensky, in 1920, was the first one to use the name of nonspecific adenitis of the mesentery, when in 3 cases he could not demonstrate bacteriological or histological tuberculous origin. Soon after him, Hewsser and Struthers published a paper, giving the same name to this pathological picture, as suggested by Wilensky. We do find some previous reports in the medical literature, as that of Dr. Brian from Paris, who describes an "hyperplastic reaction of mesenteric lymph nodes of unknown origin". Also in 1909 Quenú in France spoke of "para-appendicitis: a primitive invasion of the appendiceal lymph nodes without any lesion in the appendix".

Since those first reports of Wilensky few papers have been written about this subject and few etiological findings have been reported.

Etiology

We have to consider two general trends. One, that believes the mesenteric adenitis to be a consequence of a regional disease; and the other that considers the pathology as a result of a systemic process. In the first group, it has always been the appendix that was blamed; Adams and Olney consider a very "significant" fact, the "cure" of patients with enlarged mesenteric nodes, after appendectomy is done in these cases. Webster, as cited by Bayo, says that quite a few appendices reported as normal by the pathologist have microabscesses. If

*Read before the Mexico Regional Meeting of the American College of Gastroenterology, Mexico, D.F., 27 October 1958.

slides can be done of the complete organ this will often be found, but missed in a routine pathological study. This reminds us of Aschoff's reference to these microabscesses as "inoculation chancres of the nontuberculous mesenteric adenitis". Against Adams and Olney's idea Rosenburg and Aird said, that at least two-thirds of the patients who had large mesenteric nodes and in whom appendectomies were done, have recurrences of pain, being the picture less definite than previous to the operation. Werner and Feller in the 18th century, Virchow and lately, Mead, Foster Klein and Wilensky have given light to the studies of anatomy of lymphatic structures of the intestines and mesentery. In the typical mesenteric adenitis the juxta-intestinal ones are enlarged and not the appendiceal ones, that are located in the mesoappendix. This organ also has lymphatic drainage to the paracolic and lumbar nodes. Bockus calls attention to the fact, which every surgeon has often noted, that even with severe appendicitis, the ileocecal lymph nodes, are usually not enlarged. Wilensky thinks that if they are enlarged, it happens in rare cases due to anomalies in the lymphatic structures of the appendix.

We will consider now some theories of the group that attributes the nonspecific mesenteric adenitis to a systemic disease. Plank, in 65 cases cultivated enterococci and bacilli coli in 90 per cent of the lymph nodes obtained at operation; but he did not corroborate these findings with positive agglutination reactions.

Goldberg and Nathanson call attention to the frequent "coincidence" of an upper respiratory infection and mesenteric adenitis. In their first 8 cases, they found in one, the same streptococci in the mesenteric node and the pharynx of the patient. Wilensky agrees that after an upper respiratory infection, a small enteritis might develop (almost impossible to be identified by the surgeon) that can cause the enlargement of the mesenteric nodes. He insists, however, that regardless of the cause, once an enlargement is present, the abdominal picture becomes the important one, and should be taken in consideration for a correct differential diagnosis in acute abdominal conditions. He has proposed the name of "nonclassified mesenteric adenitis" instead of nonspecific.

There have been more opinions as to the primary cause of mesenteric adenitis and we can list them as follows: Svejcar, Barriola and Gatch consider that as the ileum has more germs than the upper intestinal tract, any intercurrent disease might cause them to become pathogenous and cause the node enlargement. Barriola proposed the name "terminal lymphoid ileitis"(?). The toxic and allergic origin has also been considered by Cecil and Christopher. Aird in England suggested that the findings of a nonspecific mesenteric adenitis could be the very first stages of a regional ileitis.

More recently (1954-1955) Girard in France and Knapp and Masshoff in Germany isolated from mesenteric nodes the so-called "Pasteurella-Pseudotuberculosa". The Germans found also that some cases (12) which didn't give a positive culture, did have a positive agglutination test. They think that it could

be possible to find more of these cases if the agglutination test is widely used and maybe the "pasteurella" is the etiological factor of the nonspecific mesenteric adenitis. Svedmyr and Kjellen in Sweden cultivated a virus somewhat similar to that of poliomyelitis, from 15 cases with mesenteric node enlargement. Positive cultures were obtained from the stools and the mesenteric lymph nodes.

Pathology

On opening the abdomen a moderate amount of clear fluid can be found, usually sterile; the mesentery is slightly edematous and hyperemic and the lymph nodes in variable number are enlarged varying in size from 1 to 2.5 cm., white-rose in color, elastic in consistency and without tendency to coalesce. No other pathology is found; unless a node has undergone suppuration; then a localized or generalized suppurated peritonitis will be present. Microscopically the lymph nodes show a moderate lymphoid hyperplasia and more or less hyperemia.

Symptoms and Signs

The disease is slightly more often seen in women; and the average age runs from 5 to 20 years. The sudden onset of generalized abdominal pain is accompanied by nausea and vomiting. The pain becomes intermittent usually intense and localized later to the right lower quadrant or periumbilical region. In half of the cases diarrhea is present. Physical findings are: restlessness, fever of 100°F to 101°F as average. A very marked abdominal tenderness and occasionally rebound tenderness, but almost never real muscular defense is found. The leucocyte count runs from 15 to 20,000, with a marked neutrophilia. As we can see, the picture is the one of an acute abdominal condition and the differential diagnosis with an appendicitis could be almost impossible.

We think it is important to insist, that the surgeon should always be able to make a differential diagnosis of the macroscopic findings at operation between this nonspecific adenitis and the ones found in tuberculosis and regional ileitis. The treatment and prognosis would be quite different in each case. He should also, always take a node for biopsy to run all the necessary tests for an accurate diagnosis and maybe also for an advancement in the knowledge of this "nonspecific adenitis".

Treatment

We cannot really talk about this subject because in the cases taken to the operating room, what did really count as treatment? Appendectomy? Antibiotics? or changes in abdominal pressure and rest? And we certainly cannot be sure of a diagnosis without the laparotomy findings.

We present 2 cases from the 6 we have diagnosed in the surgical service of the Hospital Central SCOP. These are typical pictures of the disease.

Case 1:—A 20-year old female was admitted to the Hospital Central SCOP with a severe pain in both right quadrants of the abdomen of a few hours'

duration; she has nausea, has vomited twice and since the onset of pain had 4 loose bowel movements. The patient was restless, B.P. 120/180, P. 120, T. 37.5°C (99.8°F). Tenderness was found all over the abdomen, with rebound tenderness in the lower half. A pelvic examination was negative. Leucocytes 12,500 with 80 per cent neutrophiles. The patient was operated on, finding a macroscopically normal appendix and numerous ileocecal lymph nodes, enlarged and of a hard consistency. No other pathology was found. Appendectomy was done and a node was taken for biopsy.

Pathology report:—Chronic appendicitis. Nonspecific adenitis. The patient was discharged without symptoms after 4 postoperative days.

Case 2:—A 21-year old female was admitted to the surgical service of the Hospital Central SCOP with a severe pain in the right lower quadrant, radiating to the right lumbar region, of 24 hours' duration; with nausea and vomiting. The physical examination revealed severe tenderness in the right lower quadrant of the abdomen with rebound tenderness. The rest of the physical was negative.

Leucocyte count was 21,100 with 90 per cent neutrophiles. At operation a retrocecal normal looking appendix was found; several enlarged mesenteric lymph nodes with slight edema of the mesentery. A node was taken for biopsy and an appendectomy was performed.

Pathology report:—Chronic appendicitis. Nonspecific adenitis.

After 4 postoperative days without complications the patient was discharged.

Summary

1. We think that up to date we still can consider the picture of the so-called "nonspecific mesenteric adenitis" as a very specific clinical entity. Wilensky is probably right in proposing the name of "nonclassifiable", and so, it is possible to consider a multiple etiology and our impossibility of finding the initial disease. We should remember the frequent past history of an upper respiratory infection, in nonspecific mesenteric adenitis cases.

2. If surgeons accept the fact of finding this disease in acute abdominal conditions, fewer diagnoses of "mural" and "chronic" appendicitis will be made. We think that finding mesenteric enlargements of no specific origin justifies the operation.

3. Even though we find some new bacteriological findings in the medical literature looking for an etiology, we must insist that the problem has not been solved, and research is open in this field. It is also impossible, so far, to diagnose the disease without the laparotomy findings.

4. The benign condition of the disease is apparent; not only because of the pathological findings and the benign course of the disease, but also because it has not been possible to reconcile the picture with other ones with a severe or fatal prognosis.

COMPLICATIONS OF MECKEL'S DIVERTICULUM ENCOUNTERED IN ADULT LIFE

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Binghamton, N. Y.

Over a century and a half has passed since Johann Frederick Meckel described an anomaly of the terminal small bowel that bears his name. The presence of this diverticulum is contingent on an arrest of the embryological developmental processes involving the omphalomesenteric or vitelline duct. In fetal life it is this structure which connects the intestine with the yolk sac. This pouch-like finding on the antimesenteric side of the bowel, usually the terminal portion of ileum, is the vestigial remains of faulty retrogression.

The three case histories presented in this article are of interest principally because they focus attention on the fact that surgical complications can and do occur in adult life.

Case 1:—H. W., a white male, age 50, was admitted to the hospital 8 April 1947 and discharged 18 April 1947. His chief complaint was that of epigastric pain, intermittent in type of approximately 24 hours' duration, relieved somewhat by enemas. Past medical history was irrelevant—no previous surgery of any kind having been done.

Examination of the abdomen revealed uniform tenderness and muscle guarding rather sharply limited to the entire right side, possibly slightly increased below the level of the umbilicus. Rectal examination was not helpful, no tenderness of any kind being detected. The white blood count was 16,000 with 90 per cent polymorphonuclear leucocytes; R. B. C. 3,910,000, hemoglobin 11.5 gm.

Surgical intervention was done the evening of the day he was admitted to the hospital. The abdominal cavity was opened through a right paramedian incision. There presented an omental covered mass the size of a grapefruit. As the omentum was separated, a perforated knob-sized mass attached to the small bowel, not too far from the ileocecal valve, was uncovered. This structure along with an adjacent margin of normal appearing bowel was removed between double clamps placed in a V-shaped manner beneath, without transecting the underlying portion of bowel. Interrupted chromic catgut placed in a double layer approximated the mucosal and serosal margin. The appendix, covered by an embryonic veil, was removed and the stump inverted. Before closing the abdominal wound in layers, 5 gm. of sulfathiazole powder was sprinkled in the operative area—no drain being used.

The pathological report indicated: 1. acute suppurative Meckel's diverticulitis with a point of necrosis extending through the layers of the bowel; 2. chronic appendicitis.

Postoperative convalescence was uneventful.

Case 2:–P. L., a white male, age 76 years, was admitted to the hospital 22 August 1951. For a period of years he had experienced bouts of cramp-like abdominal pain some of which required bed rest but subsided with enemas, laxatives, and other supportive measures. It is of interest to note that 50 years earlier he had had an appendectomy because of intermittent cramp-like abdominal pain.

The blood count showed 13.5 gm. of hemoglobin, with an entirely normal urinary report. X-ray study of the large bowel revealed normal findings. The x-ray films of the upper gastrointestinal tract showed an obstruction in the lower portion of the jejunum or upper ileum. These studies were done before I

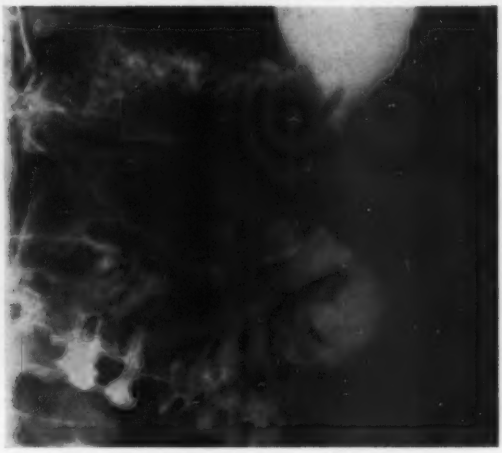

Fig. 1–Case 3, March, 1956.

was called to see him on 30 August 1951. Perhaps the barium given by mouth precipitated a more complete obstruction. With, however, the introduction of a nasogastric tube, the greater part of his abdominal distention and cramp-like pain subsided.

Surgery was performed 1 September 1951. The right-sided abdominal skin scar was excised. Freeing of the intestine started near the cecum with the short portion of collapsed ileum. A tube-like structure passing from the ileum and attached to the anterior parietal peritoneum acted like a window and through this space loops of dilated small bowel had passed. That portion of ileum containing the tube-like structure was removed between clamps and, because of the disparity in the size of the bowel ends to be anastomosed, a side-to-side, double layer interrupted chromic catgut restoration was completed.

The postoperative course was marked by a temperature elevation to 103°F. which continued for a period of approximately 48 hours, then gradually tapered to a normal level. Of more importance is that this man was disoriented for time, place and person for a period of three weeks. His mental condition then cleared and he was discharged from the hospital, with the abdominal wound well-healed and having regular bowel movements without laxatives, on 3 October 1951. (A lawyer, by profession, this man returned to his home town where he continued to practice until less than a year ago. He is now confined to a nursing home principally because of a recurrence of his mental confusion.)

The pathological examination of the specimen removed revealed: Chronic inflammation in a Meckel's diverticulum.

Case 3:—Mrs. F. K., a white female, age 54 years, was admitted to the hospital 18 March 1956 and discharged 9 April 1956. Several fainting spells

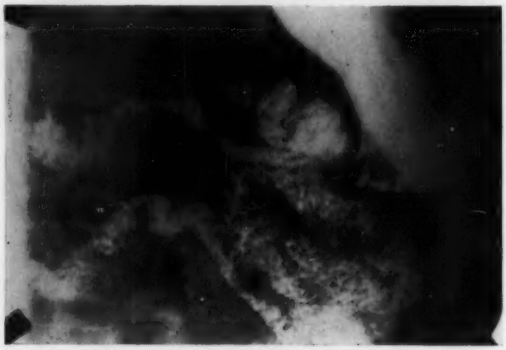

Fig. 2—Case 3, October, 1958.

followed by the passage per rectum of a large amount of clots, bright red in color, coincided with the development of an obvious pallor and an elevated pulse rate. Her past history was not too revealing, a thyroidectomy having been done by the author in 1951. For a period of about two years she had taken medication for a moderate hypertension.

Examination of the abdomen failed to reveal any areas of tenderness. None of the abdominal organs were palpably enlarged. Laboratory findings showed the hemoglobin to be 5.7 gm. per 100 c.c. of blood; the erythrocytes 1,800,000. Blood volume was restored by blood transfusions while x-ray study of the gastrointestinal tract was being done. An early sigmoidoscopic examination was noncontributory. The bowel mucous membrane appeared quite normal, there being moderately enlarged internal hemorrhoids without derangement that would indicate recent bleeding. X-ray study of the large bowel indicated the presence of one small diverticulum in the sigmoid colon. Films of the upper

intestinal tract outlined an isolated collection of barium which measured approximately 4.5 cm. in diameter, having the appearance of a diverticulum in the proximal jejunum. Restoration of the hemoglobin to 11.7 gm. erythrocytes 3,990,000 indicated that surgical exploration could be done without too great jeopardy to the patient.

Twelve days after entering the hospital she was taken to the operating room. Spinal anesthesia with sodium pentothal was administered. A retrocecal appendix was removed and the stump not inverted. Starting at the ileocecal valve the small bowel was carefully examined. There was found a diverticulum on the antimesenteric side of the bowel, the vascular pattern of the mesentery indicating jejunum. A wedge-shaped resection of that portion of the bowel with end-to-end anastomosis was done.

Postoperative convalescence was uneventful, the patient being discharged from the hospital on the ninth day.

Microscopic report of the bowel-section of jejunum with normal intestinal villi and muscularis; sections taken from the diverticulum reveal essentially a small intestinal type of mucosa, no gastric mucosa being seen.

Diagnosis:—1. obliterated fibrosis of the appendix; 2. one segment of jejunum with attached Meckel's diverticulum.

Bleeding from a Meckel's diverticulum as the presenting symptom is not an uncommon happening, particularly in infants and possibly early childhood. As a cause of bleeding in an individual 54 years of age it is seldom encountered and therefore not too frequently considered as a causative factor in bleeding from the gastrointestinal tract in an adult.

Of more importance is the location of this diverticulum high in the small bowel. The pictures taken of the x-ray films before and after surgery indicate clearly the high position of the structure. The latter picture gives convincing proof that the diverticulum detected by the original x-ray study was the "one" removed at the time of surgery.

Comment

Perforation of a hollow viscus, intestinal obstruction, and massive intestinal bleeding were encountered in the above mentioned order and while recognized clearly, the causative finding at the time of surgery came about as a surprise. Adequate removal and subsequent microscopic examination indicated inflammatory and even gangrenous mucous membrane change; but in no instance was heterotopic tissue revealed. The incidence of the heterotopic tissue in a Meckel's diverticulum approximates 15 to 25 per cent[1]. In order to explain the presence of this tissue it has been promulgated that the vitelline duct has some function associated with digestion in early fetal life. These premature endodermal cells have

the potential of developing into any type of mature cellular pattern found in the upper gastrointestinal tract. This theory is known as that of dysembryoma.

The examination of a larger portion of the ileum, starting near the ileocecal valve, at the time of removal of an appendix, which does not by its gross appearance account for the preoperative symptoms, should be routine practice. If encountered, the removal of a diverticulum, regardless of its apparent benignity is mandatory. One in every five does contain quiescent heterotopic mucosa[3]. The finding of a true diverticulum in the jejunum indicates the necessity of carefully examining a greater portion of the small bowel than the so-called "terminal ileum".

Preoperative x-ray films seldom are helpful. In Case 3, however, the x-ray diagnosis of a pouch-like structure, high in the small bowel, proved to be the causative factor of the massive intestinal bleeding (Fig. 1). The pictures of the x-ray films are of interest because they indicate very clearly that the referred to sac-like structure of roentgenological diagnosis was removed. Of more importance is that at the time of the second x-ray study, two years later, the patient had not had any recurrence of intestinal bleeding (Fig. 2).

In all three cases presented a definite diagnosis of Meckel's diverticulum based on the necessary criteria was made. "The sac must not only be on the antimesenteric border of the bowel, and be proximal to the ileocecal valve, but it must also have a separate blood supply in the form of a mesenteriolum. All layers of the small bowel must be found in the diverticular sac[3]".

The incidence of pathological change in a diverticulum approximates the reported finding of heterotopic tissue (i.e.) 15-25 per cent[2]. Chaffin, however, has reported that, "Ulceration has been demonstrated in a diverticulum where no trace of heterotopic tissue was evident[1]".

Acute perforation and intestinal obstruction occurring from changes taking place in a diverticulum usually precipitate an acute abdominal emergency. I believe this holds regarding perforation more than obstruction. In spite of chemotherapeutic and antibiotic measures, early surgical intervention is necessary if postive interruption of the offending mechanism is to be attained.

The successful use of the nasogastric and long intestinal tubes usually allows for an advantageous delay in bowel obstruction, during which time electrolyte balance can be restored and some type of x-ray study completed.

Surgical intervention, properly timed, however, will be required to determine the true nature of the causative mechanism. In massive intestinal bleeding, it is the rate of flow which is the factor of prime importance. If the leak is gradual and the time element for hemodilution sufficient, then all parties are indeed fortunate.

There occurred in Case 3 an obscure cause of massive bleeding, but the rate of flow subsided. When the initial shock responded to blood replacement,

x-ray studies were done while full blood volume was being replaced gradually over a period of several days. The rare finding, its positive removal and subsequent course of the patient make, all told, an interesting, worthwhile and revealing study.

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CARCINOID OF THE STOMACH

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The occurrence of a carcinoid tumor in the stomach is most unusual. Askanazy was credited with the first case report in 1923[2]. In 1956, Lattes and Grossi were able to collect 35 cases and they reported five of their own[4]. Muller and his associates observed one case[5]. Adamson and Postlethwait reported two[1].

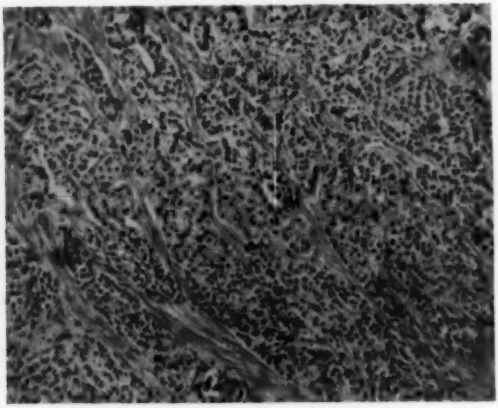

Fig. 1—Photomicrograph, moderate enlargement of carcinoid of the stomach. The neoplasm is composed of rounded masses and elongated cords of relatively uniform cells with pale, finely granular cytoplasm. The nuclei show little variation in size and in staining quality. Mitoses were not seen.

In addition, Gabrilove described a carcinoid in gastric tissue within a dermoid cyst of the ovary[3].

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Case Report

This 32-year old white female patient was admitted to the St. Joseph Hospital, Chicago on 26 April 1948, complaining of abdominal cramps and tarry stools for a period of two days. The examination revealed an anemic and slightly lethargic woman without other contributing clinical findings. The hemoglobin was 8.5 mg. per 100 ml. of blood. The laboratory data were otherwise within normal limits. X-ray examination of the upper gastrointestinal tract was negative. The working diagnosis of bleeding peptic ulcer was made and following medical management, the patient recovered. She was discharged three weeks later in good condition. She was readmitted in October of 1949 and in July of 1951 with similar episodes of upper gastrointestinal hemorrhage. Repeated x-ray examinations of the gastrointestinal tract remained negative and the patient always recovered temporarily following the conservative treatment.

The last admission followed on 30 December 1951 with the history of hematemesis two weeks prior to the admission and tarry stools for two days. The physical examination was negative except of the pale skin and mucous membranes. The red blood count was 3.7 million per cu. mm., the white cell count 11,700 per cu. mm. and the hemoglobin 11 gm. per 100 ml. of blood. The patient was treated with blood transfusions, intravenous fluids and sedatives. In spite of these measures, she continued to vomit bright red blood for two consecutive days. At this time, a surgical exploration seemed to be imperative. The laparotomy revealed a mass on the anterior wall of the stomach, in the middle third of the greater curvature. The stomach was opened and a small tumor was found protruding from the surface. The overlying mucosa was eroded with a freely pumping blood vessel in its center. Local excision of the tumor was performed. The postoperative course was uneventful.

The surgical specimen consisted of a segment of the stomach with a rounded mass in its center. The mass measured 12 mm. in maximum diameter and it was located in the submucosa. The cut surface of the tumor had a gray-white color and a finely granular character. Microscopically, it was composed of round and oval cells arranged in small solid masses and elongated cords which were separated by strands of collagenous connective tissue. The neoplastic cells had a finely granular cytoplasm with deeply staining relatively uniform nuclei. No mitoses were seen. The tumor did not extend into the muscularis (Fig. 1).

Diagnosis:—Carcinoid. An argentaffine stain was not done.

The patient was last seen in November of 1953. Following the operation, she was free of symptoms and she did not show evidence of gastrointestinal disease. Roentgenological examination of the chest and stomach failed to reveal evidence of a metastasis or of recurrence.

Comment

Carcinoids of the stomach have been reported to occur between the ages of 15 and 89 being most common during the fifth to the seventh decades. The tumor is more common in women than in men. It may be asymptomatic and an incidental finding at autopsy. In symptomatic cases, upper abdominal pain, nausea, hematemesis, tarry stools and anemia were observed. Pyloric obstruction and diarrhea were also described. Neither the clinical symptoms nor the x-ray findings are characteristic and in view of the rarity of this condition, a preoperative diagnosis cannot be made from these findings. A small tumor may be discovered only at the time of an abdominal exploration. The carcinoids of the stomach are similar to carcinoids in other locations. The small tumor is located in the submucosa, as a rule. As it increases in size, the tumor may invade the adjacent layers. Multiple foci were observed. The cut surface is firm and gray or brown in color. Microscopically, carcinoids of the stomach are similar to carcinoids in other locations. The argentaffine stain may or may not be positive. Regional and distant metastases were described in approximately one-fourth of the cases. Lattes and Grossi, however, were impressed with the slow rate of growth even in these cases[4].

Summary

Carcinoid of the stomach is a very rare, single or multiple lesion. Its natural history is similar to that of carcinoids in other locations.

The clinical findings are not specific and they simulate those of benign or malignant lesions of the stomach. Since approximately one-fourth of these tumors metastasize, all carcinoids of the stomach should be treated as potentially malignant neoplasms.

One case of carcinoid of the stomach is reported.

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CLINICAL STUDY ON THE EFFECTS OF BENZOMETHAMINE CHLORIDE

(A New Anticholinergic)

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Over the past few years, a large number of anticholinergic drugs have been released for the treatment of gastrointestinal diseases. Under influence of these drugs gastrointestinal secretions and motility diminish. These effects, however,

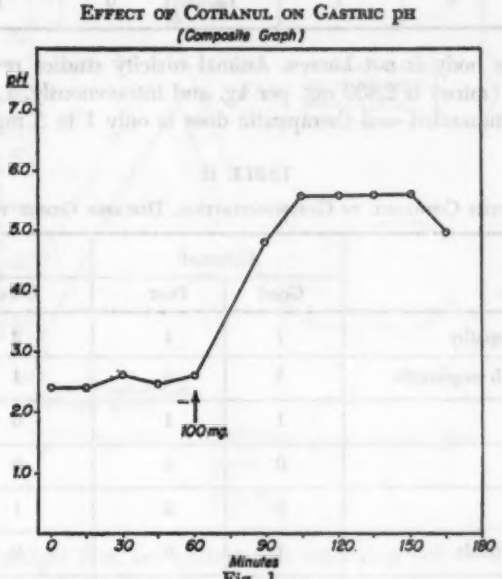

Fig. 1

are not consistent and undesirable side-effects may occur within the therapeutic range.

Benzomethamine Chloride is a new compound analagous to atropine and Banthine[1]. Its purpose, as a cholinergic blocking agent, is to suppress both excessive gastric secretion and gastrointestinal motility. In order to assess the effects on humans, two separate studies were performed.

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Pharmacology

Benzomethamine Chloride (Cotranul‡), is an anticholinergic drug with an amide linkage which confers a high atropine-like activity on the drug. It is absorbed from the intestinal tract and excreted by the kidneys[2]. Its metabolic

TABLE I

Effects of 100 mg. and 200 mg. of Cotranul on Free Acid and Volume

	100 mg.			200 mg.		
	Increase	Unchanged	Decrease	Increase	Unchanged	Decrease
Free acidity	2	2	10	1	1	7
Volume	0	1	13	0	1	8

pathway in the body is not known. Animal toxicity studies reveal that orally, the LD_{50} dose (mice) is 2,930 mg. per kg. and intravenously, 1,540 mg. per kg. Since the recommended oral therapeutic dose is only 1 to 2 mg. per kg., there

TABLE II

Results with Cotranul in Gastrointestinal Diseases Other than Ulcer

Disease	Cotranul		Placebo	
	Good	Poor	Good	Poor
Functional colonopathy	7	1	2	8
Hiatus hernia with esophagitis	3	0	1	2
Gastritis	1	1	0	1
Adhesions	0	0	0	1
Cholelithiases	0	2	1	4
Esophageal diverticula	1	0	0	0
Colonic diverticula	0	0	0	1
Prolapse of gastric mucosa	0	0	0	1
Undiagnosed	0	2	0	4

is obviously a large safety factor. Comparative toxicity studies showed that Cotranul was somewhat more toxic than atropine but less so than methantheline

‡The Stuart Company.

bromide. It has one-half the anticholinergic effect of methantheline bromide on a mg. for mg. basis[4-8].

Method

Two groups of patients were studied: hospitalized patients and ambulatory clinic patients.

1. One group of patients admitted to the hospital wards whether for gastrointestinal or other ailments were used for gastric secretion studies.

Effect of Cotranul on Free and Total Gastric Acidity

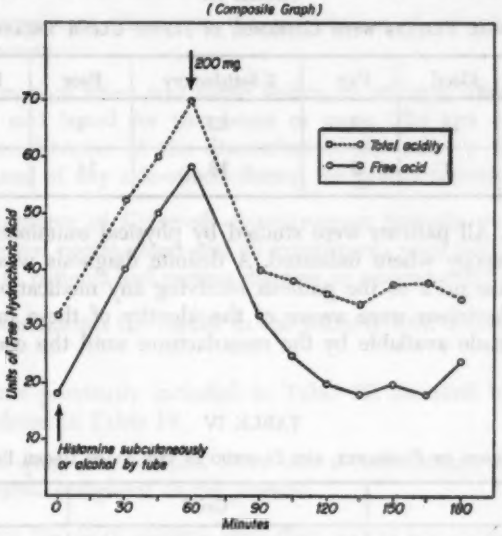

Fig. 2

After an overnight fast, the patient was intubated with a Levin tube and basal secretion aliquots were drawn every 15 minutes for one hour. Some of these patients received no stimulants, others received 50 c.c. of 7 per cent alcohol by tube and in some, histamine (1 c.c.) was injected subcutaneously at the start of the basal hour. The stimulants were given only if the basal secretion was low in acid content. Cotranul was then instilled into the tube in a liquid form in doses of 100 or 200 mg. After clamping the tube for 30 minutes, collections were continued every 15 minutes until gastric juice could no longer be obtained or until the acidity began to return to the basal level. The volume of all specimens was measured and the free acidity titrated using Topfer's reagent. In the last eight studies only the pH of the specimens obtained was measured.

We felt that not only was this a more reliable method, but it also was a necessary expedient since we frequently were unable to obtain a large enough volume to titrate the acidity after the instillation of Cotranul. Thirty-five of the studies were discarded either because the volume of the specimens obtained was too small or because hypoacidity or anacidity were found during the basal hour studies.

2. Patients attending the gastrointestinal out-patient department with known gastrointestinal disorders were used in a double-blind clinical trial of Cotranul using identical appearing coded tablets of 50 mg. active drug and

TABLE III

CLINICAL RESULTS WITH COTRANUL IN PEPTIC ULCER TREATMENT

Drug	Good	Fair	% Satisfactory	Poor	Lost to Follow-up
Cotranul	18	2	83	4	4
Placebo	1	2	18	14	0

placebo tablets. All patients were studied by physical examination, laboratory, x-ray and endoscopy where indicated. A definite diagnosis was established in almost every case prior to the patients receiving any medication. None of the participating physicians were aware of the identity of these tablets since the code was not made available by the manufacturer until the completion of the studies.

TABLE IV

COMPARISON OF COTRANUL AND PLACEBO IN THE SAME ULCER PATIENTS

Drug	Good	Poor
Cotranul	7	2
Placebo	0	9

Alternate patients received each compound, and clinical response and side-effects were tabulated at one or two week intervals. To check our clinical responses later in the study, nine patients in the ulcer group were selected at random and cross-over studies using both compounds were then carried out in these patients.

RESULTS

1. Effects on gastric secretion:—The experimental results following instillation of 100 mg. and 200 mg. of Cotranul are tabulated in Table I.

The results were the same whether no stimulus, or stimulation with histamine or alcohol was used.

It is to be noted that three patients showed an increase in total free acidity (one patient went from 20 units to 60 units). These three patients were especially apprehensive and the possibility that Cotranul had no effect in suppressing the emotional aspect of acid secretion must be considered. There was apparently no difference in occurrence of effects whether 100 or 200 mg. of Cotranul was used.

Figures 1 and 2 are composites of titration and pH curves after Cotranul instillation.

The most consistent effect was the suppression of volume to practically unobtainable amounts.

Usually, a marked effect was noted within 30 minutes. These effects gradually increased and lasted for two hours or more. The test was not carried beyond this time because of the discomfort of the tube to the patient. No patient complained of any side-effects during the gastric secretion studies.

2. *Clinical effects of Cotranul:*—Seventy-seven patients were studied. Of these 36 had proven peptic ulcers and 45 experiments were performed on them. The remaining 41 patients had various diseases as enumerated in Table II.

Table III summarizes the results in the patients with a diagnosis of peptic ulcer.

Nine patients previously included in Table III received both drugs with the results tabulated in Table IV.

It appeared quite obvious that there was a considerable difference in the efficacy of Cotranul compared to the placebo.

Table V lists the ulcer patients with their results and side-effects.

Table VI lists the results obtained with Cotranul when used in 41 patients with diseases other than peptic ulcer. (Three of these patients used both tablets).

It follows that Cotranul may well be effective in relieving functional colonic diseases and may aid in the treatment of hiatus hernia complicated by esophagitis. The former effect could hardly have been expected since anticholinergics in general do not consistently relieve these conditions. The effects in hiatus hernia with esophagitis were expected in view of the good results in suppression of gastric volume and acidity obtained with Cotranul.

With the dosage used, the side-effects were minimal and these effects almost always disappeared on continued usage. Table IV summarizes the side-

TABLE V

COMPARISON AND RESULTS OF TREATMENT OF PEPTIC ULCER WITH COTRANUL AND PLACEBO

Case Number	Diagnosis	Drug Given		Result	Side-effects				Comment
		Cotranul	Placebo		Xerostomia	Mydriasis	Constipation	Dysuria	
A 23-741	Duod. ulcer	X		Excellent					Recurred in 7 mos.
A 22-821	Duod. ulcer Antral gastrit.	X		Excellent	Slight		Slight		Side-effects disappeared on continuous treatment.
A 21-700	Prepyloric ulcer	X	X	Excellent Poor	Moderate	Slight	Slight	Slight	Relapse on placebo.
A 25-331	Duod. ulcer	X	X	Poor on both.					Large psychic overlay.
A 16-707	Prepyloric ulcer with cicatrization		X	Poor	Slight				
A 3602	Small duod. ulcer with psychosis	X		Poor					Under psycho-therapy.
A 25-586	Duod. ulcer		X	Poor					
A 12-800	Duod. ulcer	X		Good					
E.H.S. 27	Duod. ulcer	X	X	Excellent Poor					After placebo failed, he responded to Cotranul
A 22-247	Duod. ulcer	X	X	Excellent Poor	Slight Slight	Slight			Ditto.
A 19-489	Duod. ulcer		X	Poor					
A 6560	Duod. ulcer	X	X	Excellent Poor	Moderate Moderate				Ditto.
A 26-057	Pyloric channel ulcer	X	X	Excellent Poor	Marked	Marked			Side-effects with placebo only.
A 27-708	Duod. ulcer	X		Excellent					

									gone after 1 mo.
A 18-609	Duod. ulcer Gastrectomy with gastroenterostomy	X		Excellent					
A 11-078	Duodenitis	X		Good	Moderate				Relapse when Cotranul discontinued.
A 26-949	Prepyloric ulcer	X		Excellent					
A 25-832	Duod. ulcer	X		Excellent			Moderate		
A 2523	Duod. ulcer		X	Poor					Regurgitated on placebo.
A 1147	Duod. ulcer cholelithiases	X		Poor			Slight	Moder.	No relief from belladonna.
A 22-893	Duod. ulcer		X	Good					
A 26-336	Lesser curvat. ulcer	X		Excellent					Complete healing in 6 wks. by x-ray.
A 2636	Duod. ulcer cholelithiases	X		Excellent	Slight		Slight		
A 5458	Duod. ulcer		X	Poor					Required surgery
A 11-853	Duod. ulcer	X	X	Excellent Poor					Cotranul aided after placebo failed.
A 5490	Duod. ulcer	X		Excellent	Slight				
A 6697	Duod. ulcer		X	Good					
A 24-762	Gastric ulcer	X		Excellent					
A 26-170	Duod. ulcer	X	X	Excellent Poor	Slight		Moderate		Relapse when placed on placebo.
A 29-156	Duod. ulcer	X	X	Poor on both.					Required psychotherapy.
Total Results	32 (a)	24	17	(b)		(c)			

(a) four lost to follow-up
(b) see Table 2
(c) see Table 4

effects encountered with the active drug and the placebo. Other investigators have commented on the psychological effects of a placebo, even to the extent of producing severe side-effects.

Comment

In our studies, we have found that Cotranul is effective in suppressing gastric secretion; this effect is most marked on the total volume and to a slightly lesser degree on gastric acidity.

Our study was a controlled double-blind investigation since none of the investigators (including the authors) had the slightest knowledge as to which was the active tablet. Any subconscious bias on the part of the investigating physicians was therefore obviated.

TABLE VI

Side-effects of Active Drug and Placebo

	Cotranul						Placebo					
Effect	4+	3+	2+	1+	0	%	4+	3+	2+	1+	0	%
Xerostomia	0	3	6	2	29	27.5	1	3	0	4	34	19
Blurred Vision	0	0	2	2	36	10	1	0	1	0	40	4.7
Constipation	0	0	2	4	34	15	0	1	3	0	38	9.5
Urinary Difficulties	0	1	1	0	38	5	0	0	0	0	42	0

The clinical trials revealed that Cotranul is effective in the treatment of peptic ulcer with relatively few side-effects. None of the side-effects required either withdrawal of the drug or decrease in the recommended dosage of 50-100 mg. q.i.d. It remains to be seen whether those patients who are resistant to Cotranul, and have no complicating condition could be beneficial by the addition of a mild sedative or tranquilizer. The high incidence of "side-effects" with placebos would appear to support this latter point.

Theoretically, an effective anticholinergic drug could be expected to relieve patients afflicted with esophagitis secondary to hiatus hernia, by decreasing the acidity and volume of the fluid that bathes the lower end of the esophagus. In this respect, it may be of some importance that three patients with this diagnosis actually were benefited.

Of additional clinical importance is the last beneficial effect attributable to Cotranul on those functional cases commonly designated as spastic or irritable colon, but better designated as functional gastroenterocolonopathy.

Summary

Gastric secretion studies have revealed that Cotranul (Benzomethamine Chloride) is effective as an anticholinergic agent in reducing both the titer of free gastric acid and the volume of gastric secretion.

Cotranul was efficacious in the treatment of 20 of 24 patients with peptic ulcer, in 3 patients with esophagitis secondary to hiatus hernia and in 6 of 7 patients with apparently functional intestinal disorders.

Acknowledgment

The authors wish to express their appreciation to the following physicians who participated in the clinical studies:—Dr. Martin Merlis, Dr. Murray Rubin, Dr. Julian Gewertz, Dr. Rupert Taylor and Dr. Samuel Grubin.

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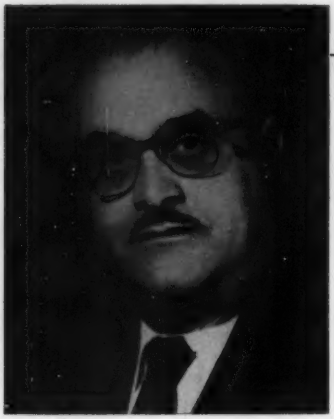


President's Message

Reservations for Our Los Angeles Convention 21, 22, 23 September 1959

It is nearing Convention time, which by the way comes one month earlier than previous years, and I would like to take this opportunity to invite all members and guests of the American College of Gastroenterology to make their reservations for hotel accommodations as soon as possible. As you know, a block of rooms have been set aside for our College and I would recommend that you write in early for rooms, specifying date of arrival and departure, so that you will not be disappointed.

Many of you and your guests are planning, I hope, to go on to Hawaii following the Convention. I would appreciate your notifying our office of your intentions now, so that proper arrangements might be made in advance.

Your over all chairman on arrangements, Dr. Donald C. Collins, has done a magnificent job to date and the Convention should be outstanding. Dr. Wharton and his committee on Program and Postgraduate Course have arranged an excellent and interesting group of scientific papers and an instructive Postgraduate Course to follow. All those attending, I am sure, will benefit greatly from this year's program.

By making your reservations for the Convention and trip to Hawaii now, you will be helping our various committees in planning for your full enjoyment of all our activities.

Frank J. Borrelli

ERRATUM

In the "Panel Discussion on Steroids in Gastroenterology" which appeared on pages 611 to 635 of our June 1959 issue, the Moderator, Dr. Murrel H. Kaplan, on page 629, referred to a recent publication by Kirsner and *Goldfarber* of Chicago.

This should have read: "Kirsner and *Goldgraber*". Our sincere apologies to Dr. Moshe B. Goldgraber for this error.

In Memoriam

We record with profound sorrow the passing of Dr. Nathan B. Jaffe of Bridgeport, Conn., Fellow of the American College of Gastroenterology. We extend our deepest sympathies to the bereaved family.

ABSTRACTS FOR GASTROENTEROLOGISTS

GASTROINTESTINAL TRACT

SUBLINGUAL CYSTS: Arnold S. Jackson. Wisconsin M. J. 57:266 (July), 1958.

Sublingual cysts are comparatively rare and are seldom reported in the literature. The author presents a short classification and differential diagnosis of sublingual cysts and suggests treatment to be surgical removal in all except hygromas where radiation should first be tried. All sublingual cysts are congenital in origin.

A. J. BRENNER

TUMORS OF THE PAROTID GLAND: Ausey H. Robnett, Milton W. Durham and Harry P. Harper. Northwest Med. 57:874 (July), 1958.

According to the author's classification two-thirds of parotid tumors are of the mixed type, a slow growing painless tumor more common in women than men. One out of 10 may be malignant. If there is a primary malignancy of the gland the entire parotid gland must be resected and radiation therapy must follow a radical neck dissection.

The low grade mucoepidermoid tumor acts as a benign tumor and may be handled as such. The high grade mucoepidermoid tumor is very malignant and the prognosis is not good for regional node metastases occurs in two-thirds and distal metastases in one-third of the cases.

Another type of tumor is the highly malignant squamous cell carcinoma, reported as composing 1.8 to 6.0 per cent of parotid tumors. Radical surgery must be done in these cases with postoperative radiation.

Roughly 10 per cent of tumors of the parotid are adenocarcinomata, which must be treated as malignant cancer.

Papillary cystadenoma lymphomatosum is a benign parotid tumor, representing about 5 per cent parotid tumors. This is an encapsulated tumor and relatively easy to remove.

Benign lymphoepithelial tumors may be diffuse in the parotid gland. These may simulate malignant tumors of the parotid gland. They may be bilateral. Radical therapy is the therapy of choice.

The authors conclude by stating that inadequate surgical treatment of tumors of the parotid is still common and is the result of a lack of understanding of the dangerous potential of parotid tumors plus fear of damage to the facial nerve.

I. HENRY EINSEL

STOMACH

ACUTE GASTRIC DILATATION: Waddy G. Baroody and Naseeb B. Baroody. Am. Pract. & Digest. Treat. 9:935 (June), 1958.

Acute gastric dilatation is to be appreciated as a serious complication of surgical and medical illnesses. The disorder is characterized by either gradual or sudden distention of the stomach with accumulation of gastric secretion and intestinal fluid which flows back from the upper gastrointestinal tract resulting in a greatly dilated and atonic organ. Initial manifestations may be minimal and transitory but may become progressively more severe with tachycardia, weakness, pallor, dyspnea, hiccough, abdominal distention, vomiting, oliguria and, finally, peripheral vascular collapse. Preceding or accompanying these findings a free flow of brown or brown-green fluid may pour from the patient's mouth—this is not true vomiting but an outpouring of fluid from the overfilled stomach in a non-expulsive manner because of increased intragastric pressure. Succussion splash is an important and easily elicited diagnostic sign of gastric dilatation.

The author uses 5 cases to demonstrate some etiological causes of gastric dilatation and the conclusion that he draws from these autopsied cases and cases where the patient improved is that the cause may be 1. electrolyte imbalance, 2. vagal stimulation, 3. mechanical and other sequela incidental to the above, 4. air swallowing with or without the "aid" of nasal oxygen, or 5. injudicious use of narcotics.

The author impresses the need of prompt treatment as a life saver.

I. HENRY EINSEL

PU-239, A POTENT NEW ANTICHOLINERGIC AGENT: R. L. Sterkel, Sr., M. Arthur Brucker and W. A. Knight, Jr. Missouri Med. 55:595 (June), 1958.

The authors assume that HCl plays an important role in the production of peptic ulcer. They state that the efficacy of reducing H+ion concentration of gastric contents is directly proportional to the neutralizing propensity of a given compound and the period allowed for interaction of the acid alkali as determined by gastric emptying time. Anticholinergic drugs seem to fulfill this basic concept. The chemical structure of the anticholinergic drugs suggests that it enters into direct competition with acetylchloride for attachment at the site of the effector cell.

At present we have in use, Darstine, Elorive, Monodral, Pamine, Pro-Banthine and Tricyllanol. PU 239 has been tried by the authors and in their preliminary report on 50 patients have found the output of free HCl in the fasting state decreased from 50 to 100 per cent. Poststimulatory output was decreased 41 to 93 per cent. There were minimal to no side-effects in patients treated with this drug in the effective dose from 10 to 40 mg. Further study is being conducted with this new anticholinergic drug now labelled as PU 239.

ABRAHAM J. BRENNER

ACUTE DISTENTION OF AFFERENT LOOP AFTER POLYA GASTRECTOMY: P. C. Watson. Brit. M. J. 5083:1334 (7 June), 1958.

Acute distention of the afferent loop is a rare but serious complication of partial gastric resection. It has been reported in connection with organic obstruction of the stoma. However, 2 cases have been observed where organic obstruction was absent and the dilatation must be attributed to a localized ileus following interruption of the vagal pathways. In one of the cases it was associated with general ileus. The

diagnosis of afferent loop distention is difficult. Continuous vomiting and upper abdominal pain are suspicious of this disorder but both may be absent. In the 2 mentioned cases the patient's general condition deteriorated a few days after surgery with tachycardia, hypotension, collapse, anxiety, restlessness, and abdominal distention. However, these symptoms are nonspecific and may be caused by peritonitis, pancreatitis, stump leakage, or intestinal obstruction. If this syndrome is suspected the passage of a nasal tube into the afferent loop may bring relief. If this procedure fails, surgical exploration with intubation of the loop under surgical guidance or enteroanastomosis are indicated.

H. B. EISENSTADT

THE EFFECT OF PROLONGED ADMINISTRATION OF RAUWOLFIA SERPENTINA (RAUDIXIN) ON GASTRIC ACIDITY: Donald Berkowitz. Am. J. M. Sc. 235:657-659 (June), 1958.

In previous studies it has been noted that reserpine when used in its usual manner for its hypotensive or tranquilizing purposes may cause a reactivation of a chronic peptic ulcer. This is a study of 25 patients taking the whole root (raudixin). Three of these patients had a history of chronic duodenal ulcer but were asymptomatic at the beginning of the study. A gastric analysis using an Ewald test meal was performed at the beginning of therapy and repeated for four months. On the basis of this relatively small number of patients the author feels that one can use up to 300 mg. of raudixin without any possibility of causing increased gastric secretion or activation of an ulcer.

BERNARD FARFEL

INTESTINES

PROCTOSIGMOIDOSCOPY AS A ROUTINE PART OF A MULTIPHASIC PROGRAM: Leonard C. Molofsky and S. Jane Hayashi. Am. J. M. Sc. 235:628-631 (June), 1958.

This is a study at the Kaiser Foundation Hospitals, in which as part of a routine examination, proctosigmoidoscopy is included routinely when the subject is older than 45 years. Thirty-seven hundred male and 3,700 female patients were examined. Amongst these asymptomatic individuals 4.51 per cent of the men and 2.27 per cent of the women had polyps. The largest number occurred in the upper rectum and rectosigmoid area. Three adenocarcinomas were found. Most of the polyps were mucous polyps and adenomatous polyps. Nine villous adenomas were discovered. It was also noted that recurrence could be expected in approximately one-third of the patients with initial polyps.

BERNARD FARFEL

NEWER CONCEPTS IN SURGERY FOR CARCINOMA OF THE COLON: John Sonneland. Northwest Med. 57:732 (June), 1958.

The author states that wide colon resection includes the following: removal of microscopic infiltration of the intestinal wall which occurs up to 7 cm. beyond the gross tumor, removal of mucosal surface contaminated with loose tumor cells, and removal of possible premalignant or malignant polyps and that lymphatic resections have been extended because of the difficulty of assessing the extent of lymph node involvement at surgery.

The surgical principles proposed are these: initially sealing the vascular channels of possible metastases before mobilization of the carcinoma, ligating the colon at points as much as 30 cm. on either side of the tumor, wrapping the tumor in an impervious shield before mobilizing the specimen, and then, coloscopy and irrigation of the remaining colon segments prior to anastomosis. The use of nitrogen mustard immediately following resection is fraught with hazards, at least in full dosage, and should probably be restricted to research cases until its value is established.

D. P. HALL

INTESTINAL OBSTRUCTION: Rudolf J. Noer. Missouri Med. 55:579 (June), 1958.

Early diagnosis and proper management is that most potent factor in reducing mortality rate in high intestinal obstruction. In the final analysis, however, one must decide the type of obstruction we are faced with and treat accordingly.

In adynamic ileus following surgery, severe infections or spinal injuries, surgery is never indicated, in fact, if an exploratory is performed in suspected obstruction and none is found enteroenterostomy once practiced should never be done. In such cases it is best to thread an intestinal tube through the pylorus and treat by suction and drainage and electrolyte support. In cases of obstruction without strangulation patient should at first be treated by suction and drainage for decompression and be given parenteral saline or blood or both if needed prior to surgical intervention.

In cases of strangulation the hazards are greater. Strangulation may be suspected by the severity of pain, rapid deterioration and deep seated constant pain persisting between cramps. Since distention of necrotic wall will cause many to perforate and develop peritonitis surgery must not be delayed. The waiting period to prepare the operating room should be utilized, however, in giving electrolytes and/or blood. A tube may be passed to relieve distention if present or to prevent distention from occurring postoperatively. Finally, one must not rely on siphonage and drainage in low or colonic obstruction. Here colostomy rather than intestinal intubation is indicated.

ABRAHAM J. BRENNER

FULMINATING, RAPIDLY FATAL SHIGELLOSIS IN CHILDREN: Dick Hoefnagel. New England J. Med. 258:1256 (19 June), 1958.

When shigellosis occurs in any members of a family, it would appear wise to obtain stool cultures from all members of the family and start treatment with sulfadiazine without delay. Children with this disease are critically ill in the course of their illness but with proper therapy, recovery is the rule rather than the exception. In the cases reported, complete postmortem examinations were available. The lack of significant pathologic findings and absence of a demonstrable cause of death were striking. Speculation outruns fact in any attempt to explain the fulminating, fatal infection described in the present series.

IRVIN DEUTSCH

LIVER AND BILIARY TRACT

PATHOLOGICAL STUDY OF THE LIVER IN KWASHIORKOR: N. K. Chanda. Brit. M. J. 5082:1263 (31 May), 1958.

There are grounds for suggesting that in kwashiorkor there may be deficiency not only of choline but also of both methionine and cystine, resulting in massive necrosis and postnecrotic cirrhosis, though the latter is of rare occurrence. Although histologically there is fibrosis of the liver in this syndrome, producing a typical picture of cirrhosis, this usually does not present as fully developed cirrhosis with hepatocellular dysfunction and portal obstruction such as is seen in infantile cirrhosis of Indian children, in which the histological picture is different, and has been described as subacute toxic cirrhosis.

LOUIS A. ROSENBLUM

STUDY OF EXTENSIONS AND METASTASES OF PRIMARY CARCINOMAS OF THE LIVER; RELATIONS BETWEEN MACROSCOPY AND HISTOLOGY OF THE CONTINGENT LESIONS: Louis Orcel. Semaine des Hopitaux de Paris, p. 371 (May-June), 1958.

Contrary to certain classical ideas, extension and metastasis are frequent in primary epitheliomas of the liver. The intrahepatic extension involves first the portal vein, particularly so in malignant hepatomas. Then vascular extrahepatic extension invades the

portal system, the cava system, and finally the pulmonary arteries.

Metastases are prevalent in the lung; they may localize in every organ and in the bone system.

Lymphatic extension is more frequent in malignant cholangiomas. It is interesting to note that these metastases sometimes appear as a phenomenon of "local differentiation" of the tumor so that hepatocellular features prevail in pulmonary localization and cholangiocellular features in ganglional metastasis, even in the case of malignant hepatoma.

Finally, the author tries to describe, in some cases, a combined systematization of the metastatic elements, principally in hepatomas.

HISTOLOGICAL FORMS OF PRIMARY CARCINOMAS OF THE LIVER IN MAN: Louis Orcel. Semaine des Hopitaux de Paris, p. 353 (May-June), 1958.

Everybody sees, in primary epitheliomas of the liver, two great groups: malignant hepatomas and malignant cholangiomas. However, several authors prefer a dual conception and consider the cholangioma as a cancer of the small biliary ducts.

The structures of the malignant hepatoma and cholangioma may be associated in the same tumor.

The distinction between hepatoma and cholangioma is sometimes difficult, when the tumor is much altered. In this case, the study of the stroma gives useful indications, in fact, this stroma is angioblastic in most hepatomas, and clearly connective and collagenous in cholangiomas.

Primary epitheliomas of the liver often present secondary alterations, partial or massive necrobiosis, clearly infarctoid in malignant hepatoma, hemorrhages and suppuration.

EARLY JAUNDICE IN THE NEWBORN: Fred H. Allen, Jr. New England J. Med. 258:1302 (26 June), 1958.

Neonatal jaundice is a major problem. Its detection depends upon visual inspection and babies less than 48 hours old should have their bassinets tagged for identification. The author advises the use of fluorescent lamps—the General Electric Company's "deluxe cool white" and "standard warm white" in a two-tube fixture which is held not more than 18 inches from the baby. He points out that yellow light makes jaundice invisible, pink light makes everyone appear jaundiced and blue light makes jaundice appear black and very hard to detect. An additional method of detecting jaundice has to do with skin blanching. He uses a piece of polished lucite with which he makes pressure upon the skin of the cheeks and forehead.

IRVIN DEUTSCH

TREATMENT OF FUNCTIONAL GASTROINTESTINAL DISORDERS WITH A LONG-ACTING ANTICHOLINERGIC-TRANQUILIZER COMBINATION: Alton D. Blake, Jr. Clin. Med. 5:773 (June), 1958.

The author has prepared a paper on the use of Combid Spansules in functional gastrointestinal orders. Combid is a mixture of Darbid, a long-acting anticholinergic, and Compazine a long-acting tranquilizer. He treated 9 cases of duodenal ulcer, 31 patients with irritable colon, 9 patients with diverticulitis and 2 each of pyloroduodenal irritability and dumping syndrome. There were few side-effects and little patient resistance because the drug only had to be taken twice a day. The results were excellent in about 89 per cent of the cases.

ABE ALPER

LIVER DAMAGE CONCURRENT WITH IPRONIAZID ADMINISTRATION: Louis Zetzel and Herman Kaplan. New England J. Med. 258:1209 (12 June), 1958.

The authors present three cases of female patients who had received Iproniazid (Marsalid) in relatively small doses, with the development of severe liver function

disturbances during the period that the drug was given. It is suggested that the hepatic dysfunction was due to this drug. This is predicated upon many previous reports of liver function disturbances as a toxic effect of Iproniazid when given in larger doses in the treatment of tuberculosis.

The liver damage in the reported cases was severe: resulting in one death, one apparent recovery after many weeks of hospitalization, and the third patient remained severely ill. In all three cases the findings of the function tests were those of hepatocellular damage. The gross and microscopic findings in the liver of the patient that died were compatible with the end stage of viral hepatitis or severe toxic liver damage as seen with cincophen, phosphorous, or carbon tetrachloride.

The liver function disturbances were inferred to be due to the Iproniazid but viral hepatitis could not be completely excluded as the underlying cause.

MORTON SCHWARTZ

CHLORPROMAZINE JAUNDICE: William F. Gebhart, Ray A. Van Ommen, Lawrence J. McCormack and Charles H. Brown. A.M.A. Arch. Int. Med. 101:1085 (June), 1958.

The liver disease caused by this drug is usually benign, but it may be protracted. Primary biliary cirrhosis with or without hypercholesteremia may be produced by thorazine. Twenty cases with chlorpromazine jaundice are reported. All were carefully examined with laboratory tests and liver biopsy. The pathological picture is characterized by the absence of cell necrosis as well as bile accumulation in the large liver ducts and bile lakes. The latter are seen in extrahepatic obstructive jaundice. Duration of the administration of thorazine to those patients ranged from 2-58 days. The smallest dose producing jaundice was 75 mg. Blood eosinophilia occurred in only 40 per cent. Alkaline phosphatase was always elevated and varied between 7 and 24 Bodanski units. Total cholesterol and cholesterol esters were also always increased. The jaundice lasted from 8 days to 10 months. The high carbohydrate, high protein, high vitamin diet with bed rest seemed to be more beneficial than steroid therapy.

H. B. EISENSTADT

PATHOLOGY AND LABORATORY RESEARCH

STUDIES ON CIRRHOSIS OF THE LIVER: IV. THE RELATIONS BETWEEN THE MORTALITY FROM LIVER CIRRHOSIS AND THE MORTALITY FROM ALCOHOLISM, AND BETWEEN THE MORTALITY FROM LIVER CIRRHOSIS AND ALCOHOLIC CONSUMPTION: Takashi Nakamura et al. Tohoku J. Exper. Med. 67:365 (25 Apr.), 1958.

From information that was available to them, the authors find a significant correlation between the mortality from liver cirrhosis and that from alcoholism. They also find correlation between the mortality from liver cirrhosis and alcohol consumption per capita in the countries of the world. They believe that the mortality from liver cirrhosis through the world depends on the degree of alcohol intake of the population. They find also from their data that there is a significant correlation between alcohol consumption and the mean annual temperature in those countries having a mean annual temperature below 16° C (60° F) whereas in countries whose mean temperature is over 16° C, there is no correlation. Lastly, they find that in the prefectures of Japan none of the correlations mentioned above are significant statistically.

PAUL B. VAN DYKE

CHLOROTHIAZIDE IN CONTROL OF ASCITES IN HEPATIC CIRRHOSIS: A. E. Read, R. M. Haslam and J. Laidlaw. Brit. M. J. 5077:963 (26 Apr.), 1958.

Chlorothiazide, 2 g. daily, was administered on 15 occasions to 13 patients with cirrhosis of the liver and ascites. On nine occasions the diuretic response was re-

garded as good; in the remaining six instances the response was poor. Refractory patients had an initial urinary sodium output of less than 1 mEq daily. Two refractory patients to chlorothiazide responded well to mersalyl.

All patients not receiving potassium supplements developed hypokalaemia. Impending or actual hepatic coma was noted in 7 of the 13 patients treated. It was usually associated with a good diuretic response to chlorothiazide and in those with a previous history of hepatic precoma. The possible mechanisms of this reaction to chlorothiazide are discussed.

Four out-patients were treated for longer periods with intermittent chlorothiazide and continuous potassium supplements. Neuropsychiatric changes were not seen, but two patients became refractory to the drug.

Continuous chlorothiazide therapy should not be given to cirrhotic patients outside hospital. Potassium chloride (3-6 g. daily) should be given to all patients with cirrhosis receiving the drug. Particular care should be taken in patients with a previous history of the neuropsychiatric complications of liver disease.

JACOB A. RIESE

PRACTICAL AND RESEARCH VALUE OF HEPATIC-VEIN CATHETERIZATION: (CONCLUDED): Carroll M. Leevy and Marvin L. Gliedman. New England J. Med. 258:738 (10 Apr.), 1958.

In a study of catheterization of the hepatic vein, the authors found the normal hepatic blood flow to approximate 1,500 ml. per minute per 1.73 square meters of body surface area with the bromsulfalein method. They point out that the hepatic blood flow varies within a wide range from person to person, regardless of the method employed. Besides bromsulfalein, the authors discuss other test substances, such as urea, galactose, and radiosotopes.

Any liver-cell damage affecting portal resistance, influences the hepatic blood flow. Protein feeding, which increases the hepatic venule wedge pressure, induces an increase in estimated hepatic blood flow in both normal and cirrhotic subjects. Fatty liver, mild or active cirrhosis and acute viral hepatitis may not markedly influence hepatic blood flow. However, a moderate to severe cirrhosis is regularly accompanied by a decrease in hepatic blood flow.

With the use of radiosotopes and hepatic-vein catheterization, information may be obtained regarding hepatic metabolism of major foodstuffs, minerals, enzymes, hormones and drugs. It has been observed that the fasting hepatic-vein glucose is normally 15 to 20 mg. per 100 ml. higher than the arterial glucose. Changes in the concentration of hepatic-vein urea provide an index to protein catabolism. Hepatic catheterization studies have shown that ammonium intoxication observed in liver disease is related to a combination of hepatic dysfunction and development of collateral circulation that causes absorbed substances to bypass the liver.

The authors further discuss the topic of hepatophlebography. Injection of contrast medium into the liver through catheterization of the hepatic vein to demonstrate the venous network of the liver has shown some value in the diagnosis of space-occupying lesions of the liver, such as cancer, cysts, abscesses and vascular anomalies.

ZACH R. MORGAN

LINKS BETWEEN INTESTINAL CHEMISM AND PARASITISM: J. Bailenger, B. Clyti and J. J. DuBarry. Arch. mal. app. dig. 47:280 (Apr.), 1958.

Establishing the frequency of parasitism for the different fecal values of the pH and the relationship between organic/ammoniac acids and amino-acids shows:

1. that for parasites of the small intestine (*Trichocephalus, Giardia*), there is a similarity with normal stools;

2. that the presence of *Endameba coli* or *Endameba hartmanni* is accompanied by alkalization;

3. that yeasts abound in acid stools.

Conclusions about the action on intestinal chemistry of other parasites could also be drawn when the results of many more coprological examinations in intestinal parasitoses have been gathered together.

GUY ALBOT

VALUE IN DIAGNOSIS OF THE MAXIMAL LIPASIC ACTIVITY OF THE DUODENAL SECRETION COLLECTED BY TUBE WITHOUT THE INJECTION OF SECRETIN: Henri Sarles, Mme. Ginette Todrani-Oswald and J. C. Sarles. Arch. mal. app. dig. 47:261 (Apr.), 1958.

Numerous methods of exploring the pancreas have been suggested. But they have often been applied to too few cases or to cases so open to question as to make it impossible for a true appraisal to be made of them. This has resulted in both unjustified approval and condemnation.

The method described here is derived from that of Chiray and Bolgert. But physiological research into secretin and pancreozymine carried out according to the main work of these authors has caused Sarles and his collaborators to simplify their exploratory method. They do not try to justify their method here, but to study its value and its limits in 151 cases where the diagnosis was certain, collected after 3,000 intubations.

Except for cancer, between 0 and 10 Bondi units one scarcely comes across anything but pancreatitis (more often than not lithogenous), papillites (perhaps most often in their early stages) and occasionally icterus due to hepatitis. The diagnostic value of the test is good in 11 out of 17 of our cases of pancreatitis which comprise this group. Between 10 and 20 units the number of pancreatitis is less; many pancreatic deficiencies which we should be tempted to call functional are due to gastroduodenal ulcers, cirrhoses, allergic dyspepsias.

From 25 to 35 units, the predominance of these syndromes is increased and the number of pancreatites decreases.

Finally at normal level pancreatitis may be found but localized in the tail of the organ or pancreatic calculi which have not yet had time to cause serious lesions.

It may therefore be seen that only a very low rate (0 to 10) has any real value in diagnosis. It is possible that Lagerlöf's secretin test is more selective, as the work of Dreiling and others would seem to show. But it seems equally likely that these authors have not been as strict as we have been in the selection of observations.

GUY ALBOT

PSYCHOSOMATIC MEDICINE

THE OCCURRENCE AND MEANING OF DREAMS OF FOOD AND EATING: Walter W. Hamburger. Psychosom. Med. 20:1 (Jan.-Feb.), 1958.

That dreams of food and eating constitute typical dreams is a conclusion based upon the analysis of 229 food and eating dreams of four female patients. This is a conclusion based upon a study of four female neuropsychotic patients and the reviewer would feel hardly represents an adequate normal sample. The author studies these dreams statistically and concludes that the prominent latent meanings are: 1. as a regressive substitute gratification for genital satisfaction and 2. as a symbol of pregenital fixations on maternal love, support and reward. The author feels that the latent symbolic meaning of foods in dreams is a rich and diverse source of psychodynamic material. The paper seems to this reviewer to be a remarkable superstructure based upon infinitesimal bits of evidence.

RALPH D. EICHHORN

RELATIONSHIP BETWEEN BENDER-GESTALT TEST SCORES AND MEDICAL SUCCESS WITH DUODENAL ULCER PATIENTS: William W. Lothrop. Psychosom. Med. 20:30 (Jan.-Feb.), 1958.

A group of 18 patients was divided into two parts; those nine patients who had successfully managed symptoms of duodenal ulcer over a period of years and a group of nine patients who were considered medically intractable. These patients were all subjected to the Bender-Gestalt Test and it was noted that both the medical and surgical failures were more deviant in their Bender-Gestalt performance than the successes. It was also noted that the scores for the medical success ranged from 15 to 57. For the medical failures the range was 58 to 112. In other words the two

groups did not overlap. This pilot study indicates that the Bender-Gestalt Test may be of value as a diagnostic device to distinguish between those ulcer patients who can be expected to respond successfully to medical treatment and those whose symptoms will be intractable.

RALPH D. EICHHORN

EFFECT OF PSYCHOANALYSIS ON THE COURSE OF PEPTIC ULCER: Samuel Z. Orgel. Psychosom. Med. 20:117 (Mar.-Apr.), 1958.

The case histories of 15 ulcer patients treated with psychoanalysis are reported. Five of them interrupted the treatment prematurely and did not obtain any benefits while the remaining 10 stayed under treatment for a period of 3 to 5 years and received between 600 to 1,000 analytic hours of treatment. These patients also had symptoms over a period of from 5 to 15 years before they underwent psychoanalysis. Five were character neuroses, 4 obsessional neuroses and 1 a mixed psychoneurosis. The patients were completely relieved from their gastrointestinal symptoms after the treatment and stayed well for a period from 11 to 22 years. There was no recurrence of the gastric symptoms. None of the patients had to stay on a diet or had to take any medications. This demonstrates that peptic ulcer is a severe emotional illness at least in a certain number of cases. The removal of the psychiatric causes of their neuroses may be able to cure their ulcer.

H. B. EISENSTADT

BOOK REVIEWS FOR GASTROENTEROLOGISTS

NUTRITION AND DIET THERAPY FOR PRACTICAL NURSES: Lillian Mowry, B.S., Chief Dietitian, Memorial Medical Center, Kansas City, Mo. 165 pages. The C. V. Mosby Co., St. Louis Mo., 1958. Price $2.50.

Although not a text book on diet therapy, this little brochure covers the subject of vitamins, diet, weights, calories, etc., adequately. It is a useful and handy reference, not only for the practical nurse, but it may also be useful to dietitians and even physicians.

HORMONE PRODUCTION IN ENDOCRINE TUMORS: G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch. and Maeve O'Connor, B.A.—Editors for the Ciba Foundation. 351 pages, 58 illustrations and cumulative index to Vols. 1-12. Little, Brown & Co., Boston, Mass., 1958. Price $9.00.

The last volume of the Ciba Foundation Colloquia on Endocrinology is a very interesting and instructive treatise dealing with the hormone production in endocrine tumors. Physiologists, research workers and endocrinologists will find a wealth of material in this treatise.

It is recommended and should prove helpful to those interested in endocrine metabolism.

THE CEREBROSPINAL FLUID, PRODUCTION, CIRCULATION AND ABSORPTION: G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Cecilia M. O'Connor, B.Sc.—Editors for the Ciba Foundation. 335 pages, 141 illustrations. Little, Brown & Co., Boston, Mass., 1958. Price $9.00.

A highly scientific treatise valuable to neurologists and neurosurgeons, but rather heavy reading for the general physician.

The print and illustrations are clear and easy to read and the book is highly recommended to anatomists and physicians dealing with the brain.

1957-58 YEAR BOOK OF ENDOCRINOLOGY: Edited by Gilbert S. Gordan, M.D., Ph.D., F.A.C.P., Associate Professor of Medicine; Chief of Endocrine Clinics, Department of Medicine, University of California School of Medicine, etc., etc., San Francisco, Calif. 381 pages, illustrated. The Year Book Publishers, Inc., Chicago, Ill., 1958. Price $7.50.

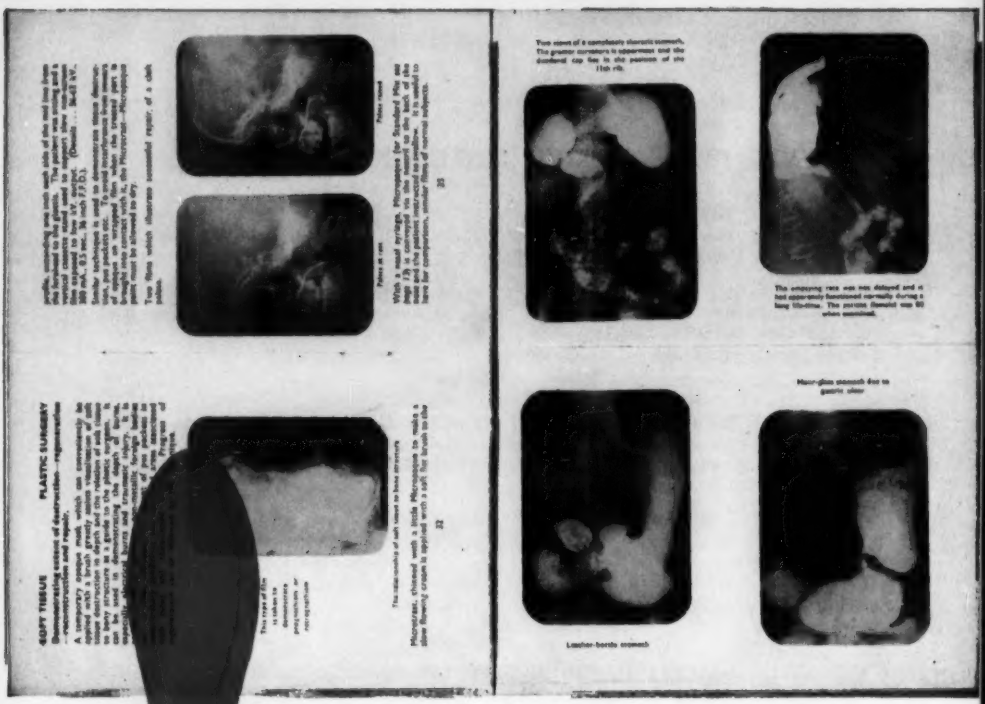
The Year Book of Endocrinology is intended as a guide rather than as a text book. It is one of the practical medicine year books and the physician will find new and useful information garnered from the world literature dealing with endocrinology and allied subjects.

On pages 17, 18, 19, 20, the reader will find abstracts dealing with the side-effects of chlorpromazine, reserpine and others on the endocrine glands. This is interesting because of the large amounts of tranquilizing agents prescribed by physicians and patients giving these tranquilizers to their neighbors without first consulting a physician.

Neurohypophysis and water metabolism on page 42, makes interesting reading. Beginning on page 51, the physician is advised to read carefully all about the thyroid gland. On page 162, carbohydrate metabolism and its congeners and aldosterone and the regulation of aldosterone secretion, are among the newer endocrinological studies which the general practitioner as well as the internist will find of interest.

Estrogens, androgens and the endocrine influences on neoplastic diseases, plus breast and other cancers add to the usefulness of this book.

A subject and author's index complete the Year Book of Endocrinology. It is highly recommended as a necessity, if the doctor wishes to keep up with modern medical knowledge.



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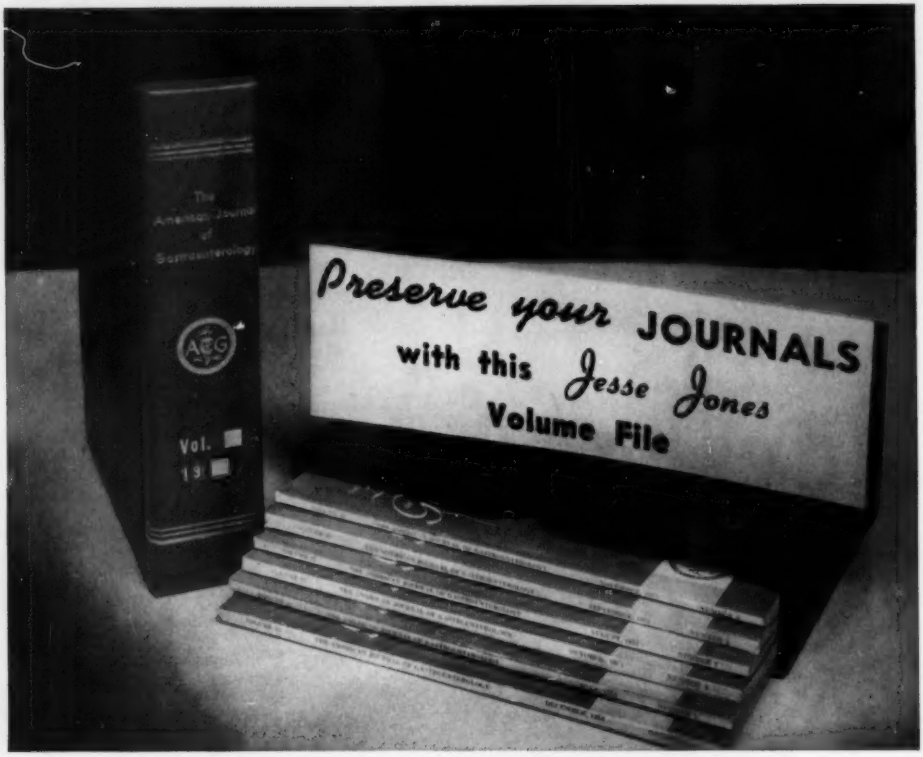

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1. Case reports on file, Wyeth Laboratories. 2. Parks, R.V., and Moessner, G.F.: Dual Approach to Patient Care, Scientific Exhibit, A.A.G.P., April, 1959.

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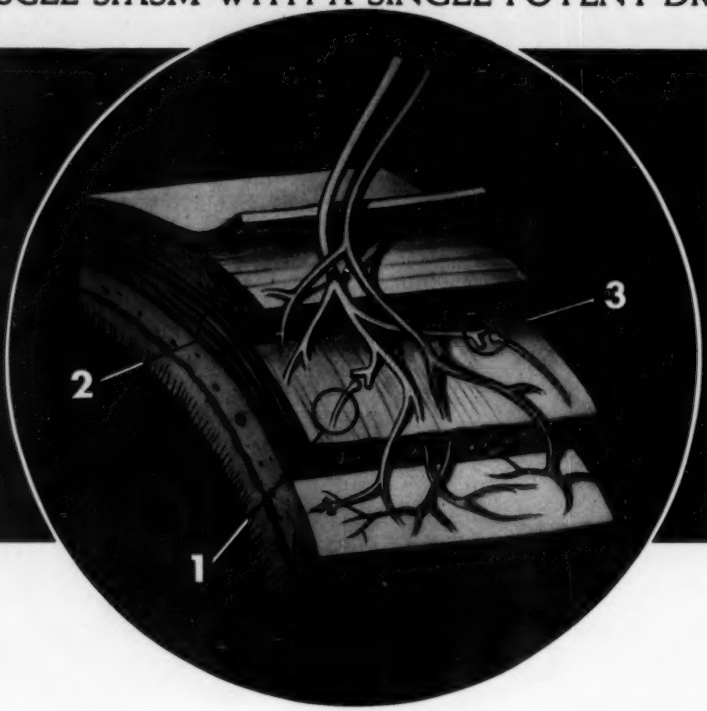

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1. Holbrook, A. A.: Report abstracted in M. Science 4:46 (July 10) 1958. 2. Peiser, U.: Med. Klin. 50:1479 (Sept. 2) 1955. 3. Winter, H.: Medizinische, p. 1206 (Aug. 27) 1955. 4. Berndt, R.: Arzneimittel-Forsch. 5:711 (Dec.) 1955.

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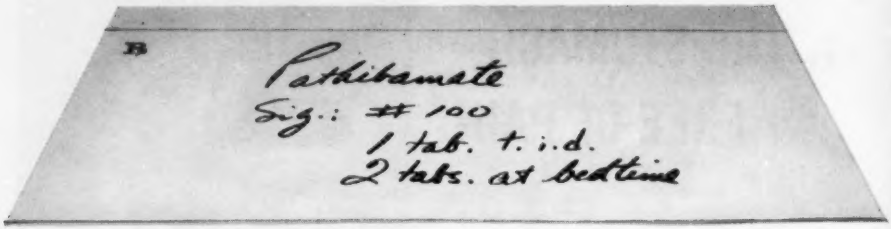

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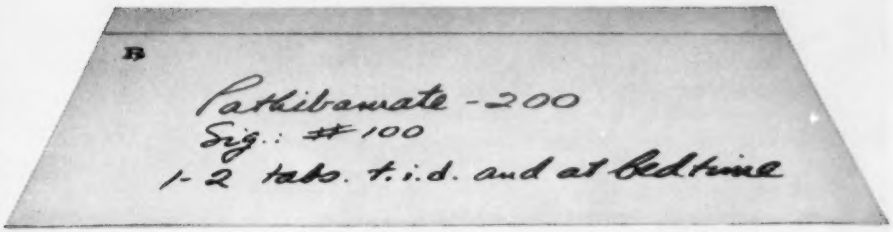

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